Janus Kinase Inhibitors for Rheumatoid Arthritis: Effectiveness and Value

Draft Evidence Report

September 26, 2019

Prepared for

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Jeffrey A. Tice served as the lead author for the report, led the systematic review and authorship of the comparative clinical effectiveness section, and wrote the background, other benefits, and contextual considerations sections of the report. Varun M. Kumar developed the cost-effectiveness model and authored the corresponding sections of the report. Laura Cianciolo authored the section on coverage policies, managed the timeline and public process, and performed quality controls. Eric Borrelli authored the section on clinical guidelines. Pamela Bradt and Steven D. Pearson provided methodologic guidance on the clinical and economic evaluations. We would like to thank Rick Chapman, Noemi Fluetsch, Foluso Agboola, David Rind, and Patty Synnott for their contributions to this report. We would also like to thank Jordan Amdahl, Rebecca Bornheimer, and Gerry Oster from Policy Analysis Inc. for their technical support with hēRo3 during the course of this review.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org.

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In the development of this report, ICER's researchers consulted with several clinical experts, patients, manufacturers, and other stakeholders. The following clinical experts provided input that helped guide the ICER team as we shaped our scope and report. None of these individuals is responsible for the final contents of this report or should be assumed to support any part of this report, which is solely the work of the ICER team and its affiliated researchers.

For a complete list of stakeholders from whom we requested input, please visit: https://icer-review.org/material/ra-update-stakeholder-list/

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No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

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Table of Contents

List of Acronyms Used in this Report

ACPA	Anticitrullinated protein antibody
ACR	American College of Rheumatology
AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike Information Criteria
CDAI	Clinical Disease Activity Index
CI	Confidence interval
CRP	C-reactive protein
CMS	Centers for Medicare & Medicaid Services
DAS28	Disease Activity Score 28
DIC	Deviance information criterion
DMARD	Disease-modifying anti-rheumatic drug
EQ-5D	EuroQol
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
evLYG	Equal Value of Life Years Gained
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index
HCPCS	Healthcare Common Procedure Coding System
IL	Interleukin
IVI	Innovation Value Initiative
JAK	Janus kinase
KM	Kaplan-Meier
LY	Life year
MDHAQ	Multi-dimensional Health Assessment Questionnaire
MRI	Magnetic resonance imaging
NMA	Network meta-analysis
NNT	Number needed to treat
OR	Odds ratio
PAS	Patient Activity Scale
PICOTS	Population, Intervention, Comparators, Outcomes, Timing, Settings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMIS	Patient-Reported Outcomes Measurement Information System
QALY	Quality-adjusted life year
RA	Rheumatoid arthritis
RAPID	Routine Assessment of Patient Index Data
RCT	Randomized controlled trial
RF	Rheumatoid Factor
SDAI	Simplified Disease Activity Index
SF-36	Short Form Survey 36
SMD	Standardized mean difference
TIM	Targeted immune modulator
TNF	Tumor necrosis factor
UK	United Kingdom
US	United States
USPSTF	United States Preventive Services Task Force
VAS	Visual analog scale
WAC	Wholesale acquisition cost
WTP	Willingness to pay

1. Introduction

1.1 Background

Background

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, affecting between 1.3 and 1.8 million Americans.[1] RA is more common in women and may occur at any age, with peak incidence occurring at ages 50-60 years.[2] RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs and skin) may be involved.[2] RA is considered a clinical syndrome that encompasses several disease subsets, each of which involves a distinct inflammatory cascade that can lead to joint damage, deformity, and organ dysfunction.[3] The course of RA may be complicated by cardiac, hematologic, and other extra-articular manifestations.[2] Historically, RA was associated with both progressive disability and a shortened lifespan, although improvements in diagnosis as well as aggressive use of disease-modifying anti-rheumatic drugs (DMARDs) have greatly improved prognosis in the past 20 years.[4]

The chemotherapeutic agent methotrexate is the most widely used conventional DMARD; it is considered an "anchor drug" because of its effectiveness and tolerability as well as its potential to enhance the effectiveness of biologic and non-biologic drugs that are targeted at certain mediators of inflammation in RA, known collectively as targeted immune modulators (TIMs).[2] However, only about 50% of patients treated with methotrexate alone will receive sufficient reduction in disease activity or remission of symptoms.[2] Over the past 18 years, the introduction of TIMs has greatly improved prognosis for many RA patients. Agents with indications for RA include inhibitors or antagonists of multiple mediators of the inflammatory cascade, including tumor necrosis factor (TNF), the B-lymphocyte CD20 antigen, interleukin (IL) 1 and 6, Janus kinase (JAK), and T cells. Guidelines from the American College of Rheumatology (ACR) recommend the use of TIMs in patients with moderate-to-severe disease activity despite the use of conventional DMARDs.[5]

In our 2017 Review, ICER assessed the relative effectiveness and value of all available TIMs at that time. Since that report two additional JAK inhibitors, baricitinib (Olumiant®, Ell Lilly and Company) and upadacitinib (Rinvoq™, AbbVie) received United States Food and Drug Administration (FDA) approval. Therefore, ICER decided to update the evidence for JAK inhibitors for adults with moderate-to-severe RA. In addition, to better reflect current clinical practice and guidelines using a treat-to-target approach,[6] we focused on measures of disease activity at three months. Patients not achieving remission or low disease activity after three months of therapy are typically switched to a different TIM.

In a separate section, we will evaluate the evidence supporting infliximab-dyyb (Inflectra®, Pfizer) as a biosimilar for the reference drug infliximab (Remicade®, Janssen) for the treatment of RA. Infliximab-dyyb is intended to serve as an exemplar to ground a discussion surrounding the relatively low penetrance of biosimilars in the marketplace despite FDA approval of more than 20 biosimilars.

JAK Inhibitors

There are currently three JAK inhibitors approved by the FDA for RA: tofacitinib (Xeljanz®, Pfizer), baricitinib, and upadacitinib. While most TIMs are biologic agents that require subcutaneous injection or intravenous infusion, JAK inhibitors are small molecules taken orally. They work by inhibiting the JAK enzymes, which mediate intracellular signaling pathways involved in the production of inflammatory cytokines, including IL-2, -4, -6, -7, -9, -15, and -21. There are four JAK subtypes (JAK1, JAK2, JAK3, TYK) that have overlapping functions. The most recently approved JAK inhibitor, upadacitinib, is supposed to be more specific for JAK1, which may influence both its benefits and harms.

Table 1.1. Dosage Forms and Administration Schedules for the JAK Inhibitors

JAK Inhibitor	Recommended Dose (mg)	Route of Administration	FDA Approval	Annual WAC
Tofacitinib (Xeljanz, Pfizer)	5 mg twice daily or 11 mg once daily (extended release form)	Oral	11/16/2012	$54,552
Baricitinib (Olumiant, Eli Lilly)	2 mg once daily	Oral	6/1/2018	$26,017
Upadacitinib (Rinvoq, AbbVie)	15 mg once daily	Oral	8/16/2019	$59,860

FDA: Food and Drug Administration, JAK: Janus kinase, mg: milligram, WAC: wholesale acquisition cost

1.2 Scope of the Assessment

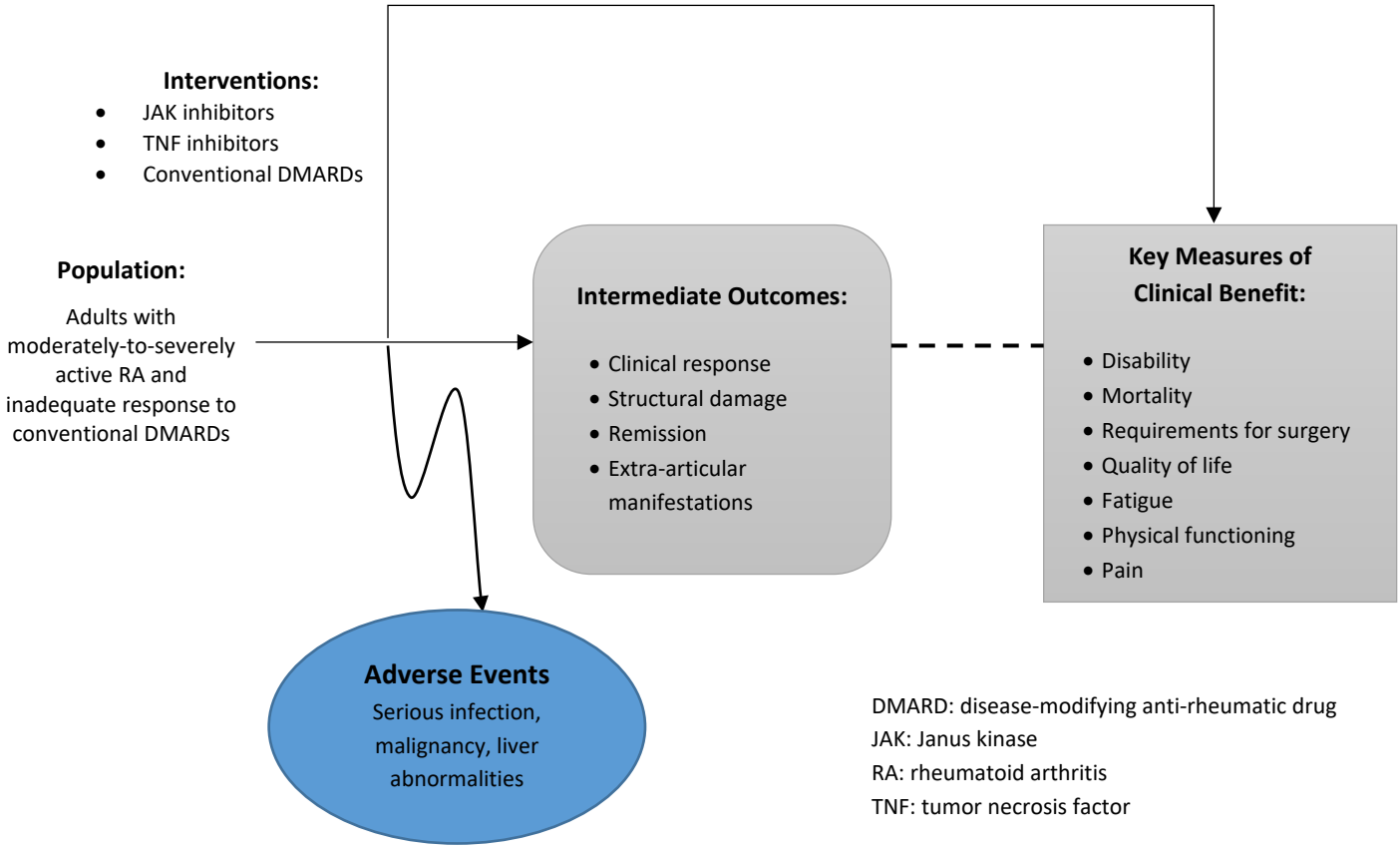
The scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was collected from randomized controlled trials (RCTs) as well as high-quality systematic reviews; high-quality comparative cohort studies were considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review includes input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Wherever possible, we sought out head-to-head studies of these interventions. We also included studies with an active comparison to conventional DMARDs or TNF inhibitors with or without conventional DMARDs. We used direct and indirect evidence in network meta-analyses (NMA) of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis are available in the Appendix.

Analytic Framework

The general analytic framework for the assessment of JAK inhibitors for moderately-to-severely active RA is depicted in Figure 1.1 below.

Figure 1.1. Analytic Framework: JAK Inhibitors for Moderately-to-Severely Active RA



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows, which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded grey boxes; those within the rounded boxes are intermediate outcomes (e.g., clinical response), and those within the squared-off boxes are key measures of benefit (e.g., disability). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of

outcomes may not always be validated. Curved arrows lead to the adverse events of treatment, which are listed within the blue ellipse.[7]

Populations

The population for the review is adults ages 18 and older with moderately-to-severely active RA and inadequate response to or intolerance of conventional DMARDs. Level of disease activity is defined according to validated and frequently used scales in RA (i.e., Disease Activity Score 28 [DAS28], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]). Note that this review will not include children, adolescents, or adults with juvenile forms of RA or other inflammatory arthritis, now collectively known as juvenile idiopathic arthritis. Feedback from patient groups and clinicians suggested that the clinical presentation and disease trajectory of these patients differs substantially from those with the adult form of RA.[8]

We looked for evidence on key subpopulations and/or data stratifications of interest. Among those suggested by stakeholders during the Open Input Period were a) evaluation of both TIM-naïve patients *and* those with inadequate response to or intolerance of initial TIM therapy and; b) use of JAK inhibitors as monotherapy and in combination with conventional DMARDs. Feedback received for our prior report indicated additional subpopulations or stratifications of interest, including a) presence of comorbidities (e.g., cardiovascular, interstitial lung disease, psychiatric, malignancy); b) both "early" (i.e., within two years of symptom onset) and established RA; c) seropositivity for prognostic markers such as anti-cyclic citrullinated peptide antibodies; d) geography, in particular US-based versus non-US settings; and e) study funding (i.e., industry-sponsored vs. other funding sources).

Interventions

The interventions of interest for this review are listed below.

- Tofacitinib
- Baricitinib
- Upadacitinib
- Biosimilar exemplar: infliximab-dyyb

We sought clinical evidence on all the products listed above. We note, however, that biosimilar data are presented separately, given differences in study design and intent (i.e., non-inferiority vs. superiority) relative to clinical studies of the originator products. We hope these biosimilar data are useful in framing a general discussion on the role of biosimilars and interchangeability status in RA.

Comparators

We examined studies comparing JAK inhibitors to conventional DMARD monotherapy or combination therapy (including triple therapy with the conventional DMARDs methotrexate, sulfasalazine, and hydroxychloroquine) to assess performance versus historical standard treatments as well as head-to-head studies between the JAK inhibitors and TNF inhibitors (adalimumab [Humira®, AbbVie] in all cases).

Finally, while studies with an active comparator arm were preferred, we also included placebo-controlled trials as necessary.

Outcomes

This review examines key clinical outcomes associated with RA. Because the recommended treat-to-target paradigm encourages switching therapy within three months for patients who do not achieve remission or low disease activity, we have prioritized measures of disease activity at that timepoint. We also expanded the outcome list based on stakeholder feedback to include additional patient-reported outcomes as well as important clinical and health care utilization measures.

- Mortality
- Treatment response (e.g., ACR20, ACR50, and ACR70, area-under-the-curve analysis)
- Measures of disease activity, remission, and remission loss (e.g., DAS28, CDAI, SDAI)
- Radiographic evidence of structural damage
- Disease-specific and general health-related quality of life (e.g., Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index [HAQ-DI], SF-36 [Short Form Survey])
- Pain (e.g., visual analog scales [VAS])
- Other patient-reported outcomes (e.g., patient satisfaction, measures of fatigue, morning joint stiffness duration and severity)
- Productivity loss and caregiver burden
- Requirements for joint replacement or other surgical intervention
- Utilization of key health care resources (e.g., hospitalization, rehabilitation, assisted living)
- Cardiovascular events
- Treatment-related adverse events (e.g., serious infection, malignancy, liver abnormalities)

Whenever possible we reported the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

Timing

Studies of three- and six-months duration were prioritized for response to therapy, but long-term evidence was preferred for harms.

Settings

All relevant settings were considered, including outpatient as well as ambulatory and hospital-based infusion centers. Several stakeholders commented on the importance of geography for our review given differences in treatment guidelines and practice patterns. We focused our attention on studies pertinent to the US setting; however, we recognized that studies conducted outside the US were useful in assessing long-term harms.

1.3 Definitions

ACR Classification Criteria (2010): Scoring algorithm for determination of definite RA based on a) number and level of joints involved; b) diagnostic serology testing; c) testing for acute-phase reactants; and d) duration of symptoms.

ACR Response Criteria: Known as ACR20, 50, or 70, representing at least 20%, 50%, or 70% improvement in tender/swollen joint counts as well as at least these levels of improvement in at least three of the following five criteria:

1) Patient global assessment
2) Physician global assessment
3) Pain
4) Disability/function
5) Acute-phase reactant values.

Historically, ACR20 was the primary endpoint in most clinical trials of RA treatments. With the advent of greater efficacy from treatment with TIMs, and with patient input about clinical significance, the ACR50 and ACR70 are also commonly included as secondary endpoints. With the shift toward treat-to-target approaches, however, measures of disease activity and/or remission are now also commonly used (see below).

Acute-phase reactants: Blood-based biomarkers for systemic inflammation characteristic of RA and other autoimmune diseases, typically C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Anticitrullinated protein antibody (ACPA): Blood test that measures the level of autoantibodies against cyclic citrullinated peptides, which are produced in excess in patients with RA. The test has been used to establish risk for RA as well as to assess disease severity and/or prognosis.

Disease activity measures: Multiple measures of disease activity, generally divided into patient-driven, patient/provider composite, and patient/provider/laboratory composite tools. All instruments differentiate low, moderate, and high disease activity:

Patient-driven tools:

- **Patient Activity Scale (PAS):** Scored 0-10 on a continuous scale based on questionnaire items regarding disability (HAQ, see below), pain, and global assessment (VAS). A second version (PAS-II) has been developed using the same format but with a different disability measure (HAQ-II).
- **Routine Assessment of Patient Index Data (RAPID-3):** Scored 0-10 on a continuous scale based on pain and global assessment VAS scales and disability measured via the multidimensional HAQ (MDHAQ).

Patient/provider composite tool:

- **CDAI:** Scored on a 0-76 continuous scale based on tender and/or swollen joint counts (up to 28 each), as well as patient and provider global VAS scores.

Patient/provider/laboratory composite tools:

- **DAS28:** Scored on a 0-9.4 continuous scale based on tender and/or swollen joint counts (up to 28 each), ESR or CRP findings, and patient global VAS score.
- **SDAI:** Scored on a 0-86 continuous scale based on tender and/or swollen joint counts (up to 28 each), CRP findings, provider global and patient global VAS score.

HAQ: 20-item RA-specific patient questionnaire designed to measure ability to perform activities of daily living in multiple domains: dressing, standing, eating, walking, hygiene, reach, grip, other activities, and requirements for assistance from devices or other persons for any of these. Also available in an abbreviated 10-item format (HAQ-II) as well as in the expanded MDHAQ that includes complex activities and psychological status.

Patient-Reported Outcomes Measurement Information System (PROMIS): Relatively new set of person-centered measures that monitors physical, mental, and social health. Early tool development has focused on neurological diseases and sickle cell anemia, and initial validation of general health questionnaires has been conducted in RA samples.[9] Instruments are not yet widely used in clinical trials, however.

Remission: Most commonly defined based on a 0 or minimal score on measures of disease activity (see above), with upper limits ranging from 0.25-1.0 on the 10-point patient-driven scales to 2.6-3.3 on the patient/provider/laboratory composite tools.

Rheumatoid Factor (RF): Blood test that measures the presence of an immunoglobulin (most commonly IgM, but can be IgG and/or IgA) that binds to IgG. The test is positive in approximately 80% of patients with RA but is not diagnostic of the disease, as a positive RF can also be seen in

other autoimmune and chronic inflammatory diseases as well as in some otherwise healthy older individuals.

Sharp Score: The most widely accepted method used to measure radiographic joint damage in RA. Multiple modifications are used, but all focus on both erosion and narrowing of the spaces between joints. The most common modifications include the van der Heijde method, which focuses on 43 areas of the hands and feet (score range: 0-448), and that of Genant, which examines 39 hand/foot areas (score range: 0-290).

1.4 Insights Gained from Discussions with Patients and Patient Groups

We received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. Patients and patient organizations advised us that health-system challenges with RA are present from the very beginning. Diagnosis is often delayed, due in large part to a shortage of available rheumatologists in many areas of the US. Even after diagnosis, coordination of care across providers and settings is problematic, particularly for patients who self-administer medication and therefore do not get the opportunity to discuss multiple aspects of their care at an infusion clinic. Perhaps in part because of coordination of care challenges, patients stressed the importance of involving family, informal caregivers, and others as a critical component for successful management of the disease.

Patients and advocacy organizations emphasized the long-term nature of the disease and the importance of both the long-term perspective and the variability in disease course and treatment changes, including drug holidays. They highlighted the importance of patient-reported outcomes and offered to help integrate them into the report and model. Multiple stakeholders recommended the inclusion of real-world data for the assessment of evidence on safety, durability of effect, and switching patterns given the widespread availability of such evidence for established therapies. Both clinicians and patient groups emphasized that their treatment goals are to achieve minimal disease activity; a 50% improvement (e.g., ACR50) is not a successful outcome for a patient with 20 active joints. These groups also highlighted the impact and burden of RA on caregivers, and suggested that both caregiver measures and outreach to caregiver groups be part of the project process. Finally, stakeholders highlighted the important progress that has been made through the use of biologics: very few patients progress to disabling joint deformities with current treatments.

Regarding treatment, we were advised that it is not uncommon for patients to cycle through various therapies before finding a treatment option to which they both respond to and tolerate; this mirrored the input received from clinicians. We also received input that "fail-first" or step-therapy insurance policies often require patients to follow a specific sequence of TIM therapies, most commonly requiring a trial of methotrexate followed by multiple attempts with TNF inhibitors. Because of the cyclical nature of the disease and its treatment, patients fear restrictions on access

to certain types of drugs, as well as more general restrictions (e.g., stopping and re-starting therapy, requirements to repeat step therapy after switching health plans, etc.).

The financial burden of RA treatment on patients and their families is also substantial. Patients did mention that manufacturers have increased their recent activity around coupons and other copayment assistance programs, but that the financial problems associated with their care remain significant and are not limited to out-of-pocket costs alone. Issues with coordination of care, navigation of insurance requirements by both patient and provider, lost time at work or school, and other challenges contribute to patient and family burden.

Patient organizations advised us that clinical trials are often lacking robust information on patient-centric outcomes, and suggested a focus on recently-developed measures such as those described in the federally-funded PROMIS toolkit (http://www.healthmeasures.net/explore-measurement-systems/promis). We revised our list of possible outcomes considerably based on this feedback. However, patients also felt that much work remains to be done on quantitative, patient-centric measures of treatment success, as many of the recent developments in defining disease remission and treatment response focus primarily on disease activity and not enough on symptom control, activities of daily living, and management of treatment-related side effects. Patients also told us that "point-in-time" measures often fail to capture the lability of RA—the disease's burden varies over time, as does the patient's ability to accommodate to the realities of the condition.

Arthritis Foundation Surveys

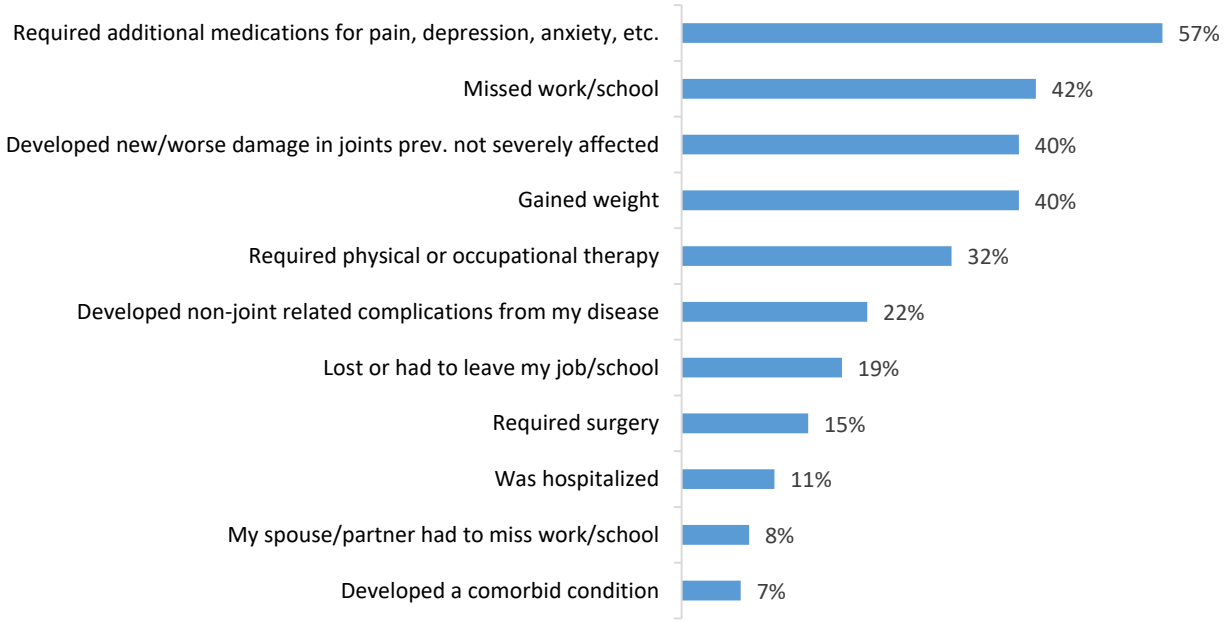
Patient Experiences

As part of their engagement with ICER during our initial 2016-17 report, the Arthritis Foundation, the leading patient advocacy group for patients with RA and other forms of arthritis, deployed an online survey during the first two weeks of November 2016 to gather information about the RA patient experience. Over 3,000 responses were recorded; a total of 1,582 individuals confirmed that they had been diagnosed with RA. The population was comparable to the demographic profile in other US-based RA cohort studies. Eighty-eight percent of RA patients were female, 83% were white (10% were African American or Hispanic), and more than half of the sample were age 55 or older (mean 59.5). Most respondents reported insurance coverage with a commercial carrier (58%) or Medicare (41%).

Experience with RA was generally longstanding—41% of the sample had been diagnosed 15 or more years ago.[10] The clinical picture for many was complex, with over one-quarter of patients also diagnosed with obesity or depression, and over 10% prevalence of comorbid cancer, heart disease, and diabetes. In addition to clinical complications, RA also has profound lifestyle impacts during periods of greater disease activity. Figure 1.2 presents impacts experienced during periods when RA was not well-controlled. Nearly 60% of patients required additional medications for pain or

mental health concerns, 42% missed some work or school, and nearly one in five had to discontinue work or school because of their condition.

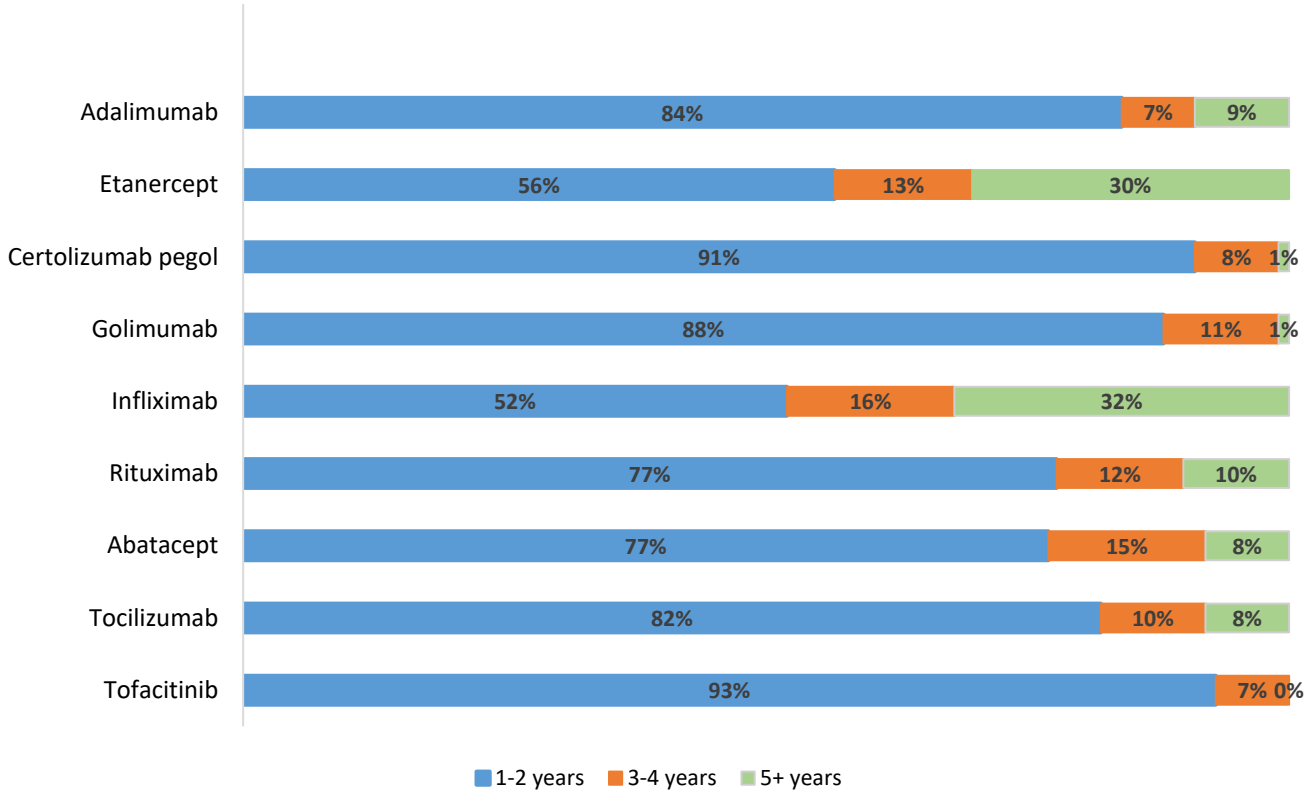
Figure 1.2. Reported Impacts of RA During Periods when Disease was Not Well-Controlled



Source: Arthritis Foundation Survey of Rheumatoid Arthritis Patient Treatment Experiences, November 17, 2016

The survey also indicated that most patients have received multiple TIMs during the course of their disease, without clearly discernible patterns regarding treatment sequence. In addition, changes in medication generally happen relatively early. As shown in Figure 1.3, while the proportions vary by TIM, 50-93% of patients are on the same therapy for only one to two years, and relatively small percentages of patients have a course of treatment that is five years or longer. The agents with the greatest proportions of long-duration users were the earliest TIMs approved for RA in the late 1990s (etanercept [Enbrel®, Amgen] and infliximab), which may be at least in part a reflection of their time on market rather than any durability advantage they hold over other TIMs.

Figure 1.3. Duration of Therapy by Type of TIM Therapy



Source: Arthritis Foundation Survey of Rheumatoid Arthritis Patient Treatment Experiences, November 17, 2016

Finally, those surveyed reported few difficulties with accessing treatment facilities or scheduling regular doctor visits, which was surprising given the reported dearth of available rheumatologists. This may be a reflection on the surveyed population (e.g., covered by employer-sponsored health insurance). However, reflecting on our conversations with individual patients and patient groups, one-third of patients reported problems with access to their medication of choice and restarting a medication they had been using if they stopped for some reason, and over 40% reported problems with care coordination across providers and settings.

Outcomes of Biologic-Naïve versus Biologic-Experienced Patients

The Arthritis Foundation deployed a second survey to assess outcomes of care in RA patients who had been treated with conventional DMARDs only for at least five years (n=222) as well as those who had received at least one TIM during this time period (n=337).[10] While findings are descriptive in nature only (i.e., not adjusted for clinical or demographic differences between groups), they echo those of cross-sectional and other observational studies that have documented the clinical effects of the introduction of TIMs. For example, while substantial proportions of both groups reported that they had experienced some level of joint damage, the proportion was statistically-significantly greater in the TIM-naïve group (90% vs. 65%, p<0.0001). Similarly, the proportion reporting at least

one joint replacement or other major orthopedic surgery (e.g., spinal fusion) was nearly three times greater among TIM-naïve patients (56% vs. 19%, p<0.0001). Finally, while disease impacts were pronounced in both patient subsets, greater percentages of biologic-naïve patients reported hospitalization or emergency room visits due to their condition/symptoms as well as receipt of disability benefits at some point.

1.5 Potential Cost-Saving Measures in RA

ICER now includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). These services are ones that would not be directly affected by therapies for RA (e.g., reduction in disability), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of RA beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with RA that could be reduced, eliminated, or made more efficient. No suggestions were received, but two of the ACR Choosing Wisely recommendations apply.[911]

Don't perform MRI of the peripheral joints to routinely monitor inflammatory arthritis.

Data evaluating MRI for the diagnosis and prognosis of RA are currently inadequate to justify widespread use of this technology for these purposes in clinical practice. Although bone edema assessed by MRI on a single occasion may be predictive of progression in certain RA populations, using MRI routinely is not cost effective compared with the current standard of care, which includes clinical disease activity assessments and plain film radiography.

Don't prescribe biologics for RA before a trial of methotrexate (or other conventional non-biologic DMARDs).

High quality evidence suggests that methotrexate and other conventional non-biologic DMARDs are effective in many patients with RA. Initial therapy for RA should be a conventional non-biologic DMARDs unless these are contraindicated. If a patient has had an inadequate response to methotrexate with or without other non-biologic DMARDs during an initial three-month trial, then biologic therapy can be considered. Exceptions include patients with high disease activity and poor prognostic features (functional limitations, disease outside the joints, seropositivity, or bony damage), where biologic therapy may be appropriate first line treatment.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

To understand the insurance landscape for treatments for RA, we reviewed publicly available coverage policies from the Centers for Medicare and Medicaid Services (CMS) and Medi-CAL, the five largest national commercial insurers (Aetna, Anthem, Cigna, Humana, and UnitedHealthcare [UHC]), and two California-based insurers (Kaiser Permanente and Health Net). At the time the Draft Evidence Report was published, we were unable to survey policies pertaining to upadacitinib because it was approved shortly before publication. Before the publication of the Evidence Report on November 7, 2019, we will survey the same insurers for coverage information about upadacitinib. We were unable to locate any National Coverage Determinations or Local Coverage Determinations for tofacitinib, baricitinib, infliximab, or infliximab-dyyb.

Impact of Plan-Level Access Restrictions on Effectiveness of Biologics Among Patients with Rheumatoid or Psoriatic Arthritis[12]

A recent publication by employees of Eli Lilly and Company suggested that some coverage policies may impact the effectiveness of biologics among patients with RA.[12] Using data on 3,993 patients from a claims database, they found non-significant trends towards a reduction in medication adherence (OR 0.90, 0.77-1.05, p=0.182) and treatment effectiveness (OR 0.93, 0.78-1.10, p=0.376) for patients with plans with access restrictions compared to those without access restrictions. These differences reached statistical significance for patients in plans with step therapy, but there was a trend toward greater adherence and greater effectiveness in patients with plans requiring prior authorization.[12] Given the small effect sizes, the small sample size, the lack of detailed patient-level data, the significant differences among patients in plans without restrictions and those with restrictions, and the lack of a propensity score adjusted analysis, these results should be interpreted with caution.

Tofacitinib

To obtain coverage for tofacitinib, most national commercial insurers require prior authorization. To obtain coverage under Aetna and Cigna, patients must be 18 years or older, diagnosed with moderately-to-severely active RA, and have documented failure, inadequate response to, or contraindication to a conventional DMARD, such as methotrexate, leflunomide, or sulfasalazine. Aetna lists tofacitinib as a one of the "least costly drugs," and neither Aetna nor Cigna require step therapy.[13]

Anthem, Humana, and UHC have more limiting policies that include step therapy that restricts coverage in ways that differ from the labeled indication of tofacitinib. In addition to documented failure, inadequate response to, or contraindication to a conventional DMARD, Anthem also requires that patients demonstrate an inadequate response or intolerance to two preferred biologics, which include etanercept, adalimumab, infliximab, and golimumab (Simponi®, Janssen). Humana's policy is comparable: patients seeking tofacitinib must have first tried and been failed by methotrexate and two preferred biologics, which include adalimumab, etanercept, and sarilumab (Kevzara®, Sanofi/Regeneron). UHC lists similar requirements for obtaining tofacitinib. Patients must first try and be failed by two preferred biologics (barring contraindications), which include certolizumab (Cimzia®, UCB), adalimumab, and golimumab. Patients can bypass step therapy requirements with a documented needle phobia.[13]

Kaiser Permanente, an integrated managed-care consortium based in California, has a less restrictive policy than most of the surveyed national commercial insurers. To obtain coverage for tofacitinib, patients must be diagnosed with RA and demonstrate intolerance to or have been failed by a conventional DMARD, such as methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide.[14] Tofacitinib is considered a Tier 4 or "specialty-tier drug" on the 2019 formulary, which means it has a higher cost share.[15] Health Net, a subsidiary of Centene based in California, considers tofacitinib medically necessary if the patient is age 18 years or old, has demonstrated intolerance to or has been failed by methotrexate, and has also been failed by separate three month trials of both adalimumab *and* etanercept.[16]

We were unable to locate a specific utilization management policy for tofacitinib under Medi-Cal, California's Medicaid program, but we note that tofacitinib is listed as a Tier 2 or "non-preferred drug" in the 2019 formulary. Tofacitinib requires prior authorization and may be subject to quantity limits.[17]

Baricitinib

The FDA label notes that baricitinib is indicated for the treatment of patients who have demonstrated an inadequate response to one or more TNF inhibitors; to that end, all national commercial insurers require step therapy in order to obtain baricitinib. All insurers first require a trial with methotrexate or a conventional DMARD, but several insurers list different preferred TNF inhibitors and vary in the number that must be tried before obtaining baricitinib.[13]

Anthem and UHC have the most restrictive policies of the national commercial insurers surveyed. In the following order, patients covered by Anthem are required to 1) try and be failed by one or more TNF inhibitors; 2) try and be failed by one or more non-TNF inhibitors or non-biologics, such as tocilizumab (Actemra®, Genentech), sarilumab, anakinra (Kineret®, Sobi), abatacept (Orencia®, Bristol-Myers Squibb), and tofacitinib, and lastly; 3) try and be failed by two preferred biologic agents, which include etanercept, adalimumab, infliximab, and golimumab. In order to obtain

baricitinib, UHC requires patients to 1) try and be failed by two preferred biologics, which include certolizumab, adalimumab, golimumab, and infliximab; and 2) try and be failed by both tocilizumab and tofacitinib. Patients can bypass step therapy requirements if they present with a documented needle phobia and are intolerant to tofacitinib.[13]

The policies of the other three national commercial insurers align closer to the labeled indication of baricitinib. Aetna requires that patients try and be failed by at least one TNF inhibitor, while Cigna and Humana require a trial of two preferred products, which include both TNF inhibitors and non-TNF inhibitors.[13]

Kaiser Permanente lists baricitinib as a Tier 4 or "specialty-tier drug" on its 2019 formulary, which means it has a higher cost share.[18] To obtain coverage for baricitinib under Health Net, patients must be age 18 years or old, have demonstrated intolerance to or been failed by methotrexate, and have been failed by separate three month trials of both adalimumab and etanercept, and tofacitinib.[16]

We were unable to locate a specific utilization management policy for baricitinib under Medi-Cal, California's Medicaid program, but we note that baricitinib is listed as a Tier 2 or "non-preferred drug" in the 2019 formulary. Baricitinib requires prior authorization and may be subject to quantity limits.[17]

Coverage Comparison of Infliximab and Infliximab-dyyb

We surveyed policies for both infliximab and infliximab-dyyb to see whether any discrepancies in coverage exist between the reference product and the biosimilar.

All surveyed national commercial insurers, except Aetna, maintain differing coverage criteria for accessing infliximab versus infliximab-dyyb. As noted above, Aetna treats infliximab and all related products (i.e., infliximab-dyyb) as preferred, least costly brands. The initial criteria for obtaining infliximab and infliximab-dyyb is identical; patients must be age 18 years or older with a documented diagnosis of active moderate-to-severe RA and must have tried and been failed by methotrexate or a comparable conventional DMARD if methotrexate is contraindicated.[13]

Anthem, Cigna, Humana, and UHC designate infliximab as the preferred product compared to infliximab-dyyb. To access infliximab under the above four insurers, patients must be age 18 years or older, have a documented diagnosis of moderate-to-severe RA, and must have tried and been failed by a conventional DMARD, such as methotrexate, sulfasalazine, or leflunomide.

However, to obtain infliximab-dyyb, the four insurers state more stringent criteria. Patients covered by Anthem must try and be failed by one preferred agent (i.e., infliximab, the reference product). If the patient is currently maintained on infliximab-dyyb, in order to continue on the biosimilar (the non-preferred brand), the patient must have undergone at least one switch between

the reference product and a biosimilar. Cigna requires that patients demonstrate intolerance to infliximab and inadequate response or contraindication to one other TNF inhibitor if they are to obtain infliximab-dyyb. Humana's criteria are similar: patients must have been failed by infliximab before accessing infliximab-dyyb. UHC lists varying criteria for obtaining infliximab-dyyb, but in most cases, patients must try infliximab for at least 14 weeks and must receive physician attestation that infliximab-dyyb would allow for a better clinical response than infliximab.[13]

Kaiser Permanente lists both infliximab and infliximab-dyyb on its Tier 4 or "specialty-drug tier."[15] However, several divisions of Kaiser Permanente, including Kaiser Permanente Colorado and Northwest, have switched patients from infliximab to infliximab-dyyb. Kaiser Permanente Colorado conducted a survey of patients who had switched to the biosimilar between September 1, 2017 and January 31, 2018, and found that 80% of patients were "satisfied" or "very satisfied" with the switch.[19] As of October 2018, Kaiser Permanente Northwest uses the biosimilar for about 97% of infliximab-related infusions, whereas infliximab biosimilars account for only 2.4% utilization across the US.[20,21]

Health Net offers slightly different criteria for infliximab and infliximab-dyyb. The only restriction for accessing infliximab is a three-month trial and subsequent failure by methotrexate or sulfasalazine, leflunomide, or hydroxychloroquine if methotrexate is contraindicated. If patients are to obtain infliximab-dyyb, they must first be failed by a three-month trial of either infliximab or golimumab.[16]

Medi-Cal does not differentiate between infliximab and infliximab-dyyb in its coverage policy. To obtain either the biosimilar or the reference product, patients must submit documentation that demonstrates medical necessity and intolerance to or failure by a conventional DMARD.[22]

2.2 Clinical Guidelines

***2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis*[5]**

The ACR guidelines were last updated in 2015 and were written prior to the FDA approval of baricitinib and upadacitinib. As an overarching principle, the guidelines note that treatment decisions should be made through a shared decision-making process between the clinician and patient. Any treatment decision should factor in patient preference and comorbidities.

In patients with RA who are conventional DMARD-naïve, the guidelines recommend the use of conventional DMARDs as monotherapy regardless of disease activity. If disease activity remains moderate or high despite utilization of conventional DMARDs, the use of a TNF inhibitor as monotherapy is recommended over tofacitinib monotherapy; in addition, the use of a TNF inhibitor plus methotrexate is recommended over tofacitinib plus methotrexate.

In patients with established RA who have moderate or high disease activity and are naïve to conventional DMARDs, conventional DMARD monotherapy is recommended over tofacitinib or conventional DMARD combination therapy. If disease activity remains moderate or high despite conventional DMARD monotherapy, the use of combination therapy or the addition of TNF inhibitor or non-TNF inhibitor, or tofacitinib is recommended in no particular order of preference, rather than continuing conventional DMARD monotherapy. For patients on a TNF inhibitor with persistently moderate or high disease activity, the use of a non-TNF inhibitor is recommended over the use of another TNF inhibitor with or without methotrexate, and tofacitinib with or without methotrexate. For patients on a non-TNF inhibitor with moderate or high disease activity, the use of another non-TNF inhibitor with or without methotrexate is recommended over the use of tofacitinib with or without methotrexate. If patients on multiple sequential TNF inhibitor therapies continue to experience moderate or high disease activity, the use of a non-TNF inhibitor with or without methotrexate is preferred over tofacitinib or another TNF inhibitor with or without methotrexate. If disease activity still remains moderate or high, the use of tofacitinib with or without methotrexate is recommended over another TNF inhibitor with or without methotrexate.

For RA patients with congestive heart failure, the use of combination DMARDs, non-TNF inhibitors, or tofacitinib is recommended over TNF inhibitors.

EULAR Recommendations for the Management of Rheumatoid Arthritis with Synthetic and Biological Disease-Modifying Antirheumatic Drugs: 2016 Update[23]

The EULAR guidelines were last updated in 2016. Similar to the ACR guidelines, the EULAR guidelines state that that treatment should be an individualized and shared decision between clinician and patient. Treatment decisions should be determined by patient-specific factors as well as disease activity.

For patients on conventional DMARDs with poor prognostic factors and who have not met their treatment target, a biologic agent or a JAK inhibitor should be considered as an add-on therapy to the treatment regimen. Biologic agents and JAK inhibitors should be combined with conventional DMARDs for superior clinical effectiveness. As a clarification, however, biologic agents and JAK inhibitors should not be used concomitantly. Patients who are failed by either a biologic agent or a JAK inhibitor should consider switching to different biologic agent or JAK inhibitor.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our analysis of the comparative clinical effectiveness of JAK inhibitors for patients with moderately-to-severely active RA who experienced an inadequate response to previous methotrexate or other conventional DMARD therapy, we abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form. The drugs and regimens of interest are included in Table 1.1 in Section 1. After the evaluation of the JAK inhibitors, there is a section describing the evidence for the biosimilar exemplar infliximab-dyyb to inform a discussion of biosimilars as part of the Policy Roundtable at the public meeting.

As described in Section 1, we focused on evidence on the comparative clinical effectiveness of JAK inhibitors in the target population (i.e., moderate-to-severe disease with inadequate response to or intolerance of conventional DMARDs).

Our review focused on key clinical outcomes common to RA trials, as well as patient-reported outcomes, health care system utilization, and work loss where evidence was available.

Clinical Benefits

Trial outcomes preferred at three months:

- Disease activity (DAS28, SDAI, CDAI)
- ACR20/50/70 response
- Function (HAQ-DI)
- Radiographic progression (modified total Sharp score)

Patient-reported outcomes:

- Health-related quality of life (e.g., SF-36)
- Pain
- Fatigue

Non-Clinical Benefits

- Health care system utilization and associated costs
- Productivity

Harms

- Treatment-related adverse events (e.g., deaths, rates of infection, malignancies)
- Treatment tolerability (e.g., discontinuation due to adverse events)

3.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on JAK inhibitors for RA followed established best research methods.[24,25] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[26] The PRISMA guidelines include a checklist of 27 items, which are described further in Appendix Table A1.

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data (https://icer-review.org/use-of-in-confidence-data/).

Study Selection

We included evidence from RCTs, comparative observational studies, and high-quality systematic reviews of JAK inhibitors and infliximab-dyyb. We excluded single-arm studies as well as early clinical studies focused on very short-term tolerability; Phase II studies were included if they reported on outcomes of interest and met other specified selection criteria. We required studies to include minimum total sample sizes of 100 and 1,000 for RCTs and observational studies, respectively. Our sample set was further limited to studies with at least three months duration of follow-up for adequate surveillance of outcomes. However, long-term extension studies that evaluated outcomes more than three years after comparator-arm crossover was allowed were excluded, given challenges with attributing study findings to initial treatment.

Study comparisons must have been between active agents: we excluded trials in which the only comparator was placebo without background methotrexate or another conventional DMARD, as well as studies that pooled individual agents into a single treatment arm (e.g., TNF inhibitors). We also excluded studies that only compared combination therapy (JAK inhibitor plus conventional DMARD) to monotherapy with the same TIM, but we did include data on both TIM monotherapy and combination therapy from trials with a third arm that represented conventional DMARD therapy alone. Biosimilar studies of infliximab-dyyb were included if they involved comparisons between the biosimilar and reference product and focused on the outcomes of interest; studies examining only pharmacodynamics or pharmacokinetics were excluded. Finally, we only included data from the FDA-approved dosage(s) for each drug.

In recognition of the evolving evidence base for RA, we supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature that met ICER standards for review (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We excluded abstracts that reported data available in peer-reviewed publications as well as abstracts on therapies that have been on the market in the US for at least three years. Further details on the search algorithms, methods for study selection, data extraction, quality assessment, assessment for publication bias, and our approach to meta-analyses are available in Appendix A.

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[27]

The matrix is meant to be a consistent, transparent system leading to an evidence rating that can guide coverage and formulary placement decisions.

Data Synthesis and Statistical Analyses

Evidence tables were generated based on the data abstracted above and are presented descriptively in the sections that follow (see Appendix D). In addition, because the treatments of interest have not usually been directly compared, we developed quantitative, indirect comparisons among all agents using a Bayesian NMA for ACR response outcomes. There was not sufficient evidence to form a network for measures of disease activity. Consistent with prior published methods,[28] ACR20/50/70 response outcomes from clinical trials were tabulated to create numbers of patients in mutually exclusive categories (i.e., <20, 20-49, 50-69, ≥70); these data were analyzed using a random-effects, multinomial likelihood model to generate proportions of patients in each category. An adjusted model was specified with a covariate for conventional DMARD response

rates as a possible control for between-study heterogeneity and general confounding. The NMA was conducted using JAGS software (version 4.3.0) via R using the R2jags package.

3.3 Results

Study Selection

Our literature search identified 540 potentially relevant references (see Appendix A, Figure A1), of which 39 met our inclusion criteria. In total, we included 39 reports of 16 RCTs. Primary reasons for study exclusion included the use of regimens or dosing schedules not approved by the FDA, study populations that included patients who were naïve to methotrexate and/or other conventional DMARDs, and smaller sample sizes (<100 for RCTs or <1,000 for observational studies). Additional details of the included references are described in Appendix D

The 16 RCTs provided data on more than 7,000 patient enrollments. Of these RCTs, six focused on JAK inhibitor combination therapy with methotrexate or other conventional DMARDs in TIM-naïve or predominantly naïve (80% or more) populations and four focused on JAK inhibitor combination therapy with methotrexate or other conventional DMARDs in TIM-experienced patients. The remainder focused on monotherapy.

We identified a total of three RCTs that involved head-to-head comparisons of JAK inhibitors with a TIM, all with adalimumab.

The search identified one randomized trial of infliximab-dyyb for RA and one prospective cohort study.

Quality of Individual Studies

We rated 15 trials to be of good (94%) and one poor (6%) quality using criteria from the US Preventive Services Task Force (USPSTF).[29] Trials of good quality had study arms that were comparable at baseline, employed valid instruments to evaluate outcomes, and did not demonstrate differential attrition. The poor-quality study did not report on randomization methods, allocation concealment, or blinding, and was much smaller than the other studies.

Most of the trials permitted use of rescue medication as early as three months following randomization, and treatment-arm crossover was often allowed at three months. While these trials had good internal validity during the pre-crossover period, extrapolation to longer-term effects poses challenges. Thus, we have emphasized the three-month outcomes. In addition, because some measures (e.g., radiographic progression) are relatively insensitive to short-term changes, these required imputations due to crossover effects or missing data.

Outcome-Specific Considerations

Our discussion of results is focused on the major clinical and functional outcomes of the available studies, including measures of disease activity and remission, ACR response, radiographic progression, and function or disability. Given the current treat-to-target paradigm, remission or low disease activity at three months is given priority. Specific considerations regarding these measures are described below.

DAS28-ESR was the most frequent measure of disease activity across all trials, reported in about 80% of the trials that included disease activity measures. Other types of disease activity measures reported less frequently included DAS28-CRP, CDAI, and SDAI. Most studies used remission rates as one of the study endpoints, defined as DAS28 score ≤2.6, SDAI score ≤3.3, or CDAI score ≤2.8. They also report low disease activity, defined as DAS28 score ≤3.2, SDAI score ≤11, or CDAI score ≤10. Low disease activity may be the most relevant under the treat-to-target paradigm in which treatment switching is encouraged within three months for patients with ongoing moderate-to-severe disease activity.[6] Given the multiplicity of measures as well as their evolution over time, we opted to describe our findings in descriptive fashion only rather than conduct an NMA. In studies that report all four measures, rates of remission and low disease activity with DAS28-ESR are consistently lower than those assessed with DAS-CRP. Disease activity and remission using SDAI or CDAI are usually comparable.

As noted in Section 1 of this report, the ACR response criteria represent at least 20%, 50%, or 70% improvement in the core measures of RA activity. The primary endpoint in the majority of RCTs included in our analysis set was ACR20. However, ACR20 is generally considered minimal improvement, while ACR50/70 are regarded to be more clinically significant levels of response.[30] We present findings for all levels of response and note where results are similar or inconsistent across these levels.

Structural damage is most commonly assessed using the Sharp score. The Sharp score sums measures of both joint erosion and joint space narrowing across several joints in the hands, wrists, and feet (the Van der Heijde modified Sharp score includes an analysis of several joints in the feet, although other approaches focus solely on the hands). The score has been modified and adapted over time, with iterations from Van der Heijde[31,32] and Genant[33] appearing most commonly in our review.

However, within the studies included in our review, the Genant and Van der Heijde methods were not applied consistently. Maximum possible scores were frequently not specified by trial investigators, and across the studies that did provide detail on the maximum achievable score, there was considerable variation (e.g., total scores using the Van der Heijde method ranged from 380 to 448).[34,35] Consequently, there is substantial uncertainty in the degree of comparability of results between studies. Furthermore, because radiographic progression occurs gradually over

time, this outcome is most frequently reported after at least 12 months of follow-up. Trials that permit early escape and/or crossover must extrapolate how much joint damage would likely occur had the patient continued with the initial treatment. These imputations are often based on a very short duration of observation (e.g., 16 weeks) and may underestimate the true progression that patients would experience had no adjustment to their therapy occurred. Missing or post-rescue therapy data were typically imputed using linear extrapolation of data from baseline and post-baseline radiographic assessment timepoints. Finally, we note that in addition to issues of multiple methods and variants to assess radiographic progression all such measures rely on clinician interpretation of radiographic data.

The HAQ-DI, a patient completed disability assessment, was the most widely reported measure of function in most studies we identified. HAQ-DI scores ranges from 0 to 3, with higher scores indicating greater disability. In many published trials, a change of 0.22 in the HAQ-DI score,[36] or a more stringent 0.3,[37] is considered a minimum clinically important difference.

Clinical Benefits

Because our study entry criteria involved patient populations with an inadequate response to conventional DMARD therapy, it is unsurprising that the results of conventional DMARD-controlled studies consistently favored JAK inhibitors for all major outcomes. As noted above, our focus of attention in the report is on the measures of disease activity/remission, as well as ACR response, radiographic progression, function/disability, and harms. A summary of other outcomes (e.g., pain, fatigue, quality of life) can be found in Appendix D.

The results are organized by indication. First, we consider patients who are predominantly TIM naïve. Some of these trials included up to 20% of patients who had failed a TIM (see Appendix D for details). Since baricitinib is not indicated for this population, no trials of baricitinib were included. Findings from head-to-head studies of the JAK inhibitor with adalimumab are also presented for the population of TIM-naïve or mixed population. In the second section, we consider the TIM-experienced population. There were no head-to-head trials for this indication. For each JAK inhibitor, we describe results according to their use in combination with conventional DMARDs.

TIM-Naïve/Mixed Populations

Comparisons to Conventional DMARD Therapy

Both upadacitinib and tofacitinib generated superior improvements in disease activity, remission, and ACR response relative to conventional DMARD therapy alone in TIM-naïve/mixed populations at 12 weeks. These results were consistent when reported at 24 and 48 weeks. Radiographic progression was also reduced, but differences in measures used made comparisons across studies difficult. Improvements in function and disability were statistically superior for both upadacitinib

and tofacitinib. A greater proportion of patients receiving JAK inhibitors met clinically important thresholds for HAQ-DI change.

A total of six RCTs compared combination therapy with JAK inhibitors plus conventional DMARD therapy with conventional DMARDs alone in TIM-naïve or mixed populations. In addition, a pooled study of randomized trials of tofacitinib reported 12 week outcomes that were not reported in the primary studies, so those results are included here as well.[38] The proportions of patients achieving low disease activity or remission at 12 weeks were substantially greater in the JAK inhibitor groups relative to conventional DMARDs alone (Table 3.1). Results achieved statistical significance for both upadacitinib and tofacitinib. It is challenging to compare the results of upadacitinib to tofacitinib as studies of upadacitinib primarily reported the DAS28-CRP, while the studies of tofacitinib used the DAS28-ESR, which generally estimates that a lower proportion of patients achieve remission or low disease activity compared with the DAS28-CRP. In addition, the primary tofacitinib trials rarely reported 12-week outcomes, though they are presented in the pooled study. When measured with the CDAI or SDAI, approximately 40% of patients treated with upadacitinib plus a conventional DMARD achieve at least low disease activity (NNT 2.5) compared with approximately 33% of patients treated with tofacitinib plus a conventional DMARD (NNT 3). Note that these results should not be directly compared as there is likely some degree of selection bias in the patients studied and we were unable to perform an NMA with the available results.

Table 3.1. Disease Activity Outcomes of JAK Inhibitors and Comparators in TIM Naïve/Mixed Patients at 12 Weeks/Three Months

Treatment	N	DAS28-ESR or CRP	DAS28 Change from Baseline (Mean)	DAS28 Low Disease Activity (%)	DAS28 Remission (%)	CDAI Low Disease Activity (%)	SDAI Low Disease Activity (%)
SELECT-COMPARE[39]							
Upadacitinib + MTX	651	DAS28-CRP	NR	45*	29*	40*	40*
Adalimumab + MTX	327	DAS28-CRP	NR	29	18	30	30
Placebo + MTX	651	DAS28-CRP	NR	14	6	16	15
SELECT-NEXT[40]							
Upadacitinib + MTX	141	DAS28-CRP	NR	48*	31*	40*	42*
Placebo + MTX	79	DAS28-CRP	NR	17	10	19	19
ORAL Sync[41]							
Tofacitinib + MTX	315	DAS28-ESR	NR	NR	8*	NR	NR
Placebo + MTX	159	DAS28-ESR	NR	NR	0.5	NR	NR
ORAL Standard[42]							
Tofacitinib + MTX	204	DAS28-ESR	NR	NR	NR	NR	NR
Adalimumab + MTX	204	DAS28-ESR	NR	NR	NR	NR	NR
Placebo + MTX	108	DAS28-ESR	NR	NR	NR	NR	NR
ORAL Strategy[43]							
Tofacitinib + MTX	376	DAS28-ESR	NR	NR	NR	NR	NR
Adalimumab + MTX	386	DAS28-ESR	NR	NR	NR	NR	NR
ORAL Scan[44]							
Tofacitinib + MTX	321	DAS28-ESR	NR	NR	NR	NR	NR
Placebo + MTX	160	DAS28-ESR	NR	NR	NR	NR	NR
Pooled Tofacitinib Trials[38]							
Tofacitinib + MTX	1,043	DAS28-ESR	NR	16.6*	7.3*	32.4*	34.6*
Placebo + MTX	638	DAS28-ESR	NR	4.5	2.3	14.3	14.2

CDAI: Clinical Disease Activity Index, CRP: C-reactive protein, DAS28: Disease Activity Score 28, ESR: erythrocyte sedimentation rate, MTX: methotrexate, NR: not reported, SDAI: Simplified Disease Activity Index
*p<0.001.

The percentages of patients achieving ACR response at 12 weeks was also statistically-significantly greater for JAK inhibitors in combination with conventional DMARDs versus conventional DMARDs (Table 3.2 below). This was true not only for ACR20 response (the primary endpoint in most studies), but for ACR50 and 70 as well. There were no marked differences in ACR responses between upadacitinib and tofacitinib across the trials, though the changes in HAQ-DI scores were slightly greater for upadacitinib. Again, these comparisons are not head-to-head and are subject to potential selection and measurement bias. The results of our NMA for ACR categories are summarized in Table 3.3 below. The results for tofacitinib and adalimumab are very similar and those for upadacitinib are slightly better (more patients in the ACR50 and 70 categories, fewer than

ACR20). All three TIMs had markedly better results than continuing conventional DMARDs alone in patients who had failed conventional DMARDs.

Table 3.2. ACR20/50/70 and HAQ-DI Outcomes of JAK Inhibitors and Comparators in TIM Naïve/Mixed Patients at 12 Weeks/Three Months

Treatment	N	ACR20 (%)	ACR50 (%)	ACR70 (%)	Change in HAQ-DI	HAQ-DI Improved ≥0.22 (%)
SELECT-COMPARE[39]						
Upadacitinib + MTX	651	71*	45*	25*	-0.60*	NR
Adalimumab + MTX	327	63	29	13	-0.49	NR
Placebo + MTX	651	36	15	5	-0.28	NR
SELECT-NEXT[40]						
Upadacitinib + MTX	141	64*	38*	21*	-0.61*	74*
Placebo + MTX	79	36	15	6	-0.26	52
ORAL Sync[41]						
Tofacitinib + MTX	315	56*	27*	9*	-0.44*	NR
Placebo + MTX	159	27	9	2	-0.16	NR
ORAL Standard[42]						
Tofacitinib + MTX	204	61.2†	34.2†	12.1†	-0.55*	NR
Adalimumab + MTX	204	56.5	23.9	8.4	-0.49	NR
Placebo + MTX	108	29	10.8	1.2	-0.24	NR
ORAL Strategy[43]						
Tofacitinib + MTX	376	70.9	40.8	19.3	-0.54	NR
Adalimumab + MTX	386	69.3	37.5	14.3	-0.49	NR
ORAL Scan[44]						
Tofacitinib + MTX	321	NR	NR	NR	-0.40*	NR
Placebo + MTX	160	NR	NR	NR	-0.15	NR
Pooled Tofacitinib Trials[38]						
Tofacitinib + MTX	1,043	60.3*	32.7*	12.9*	NR	52.9*
Placebo + MTX	638	26.5	9.7	2.8	NR	28.7

ACR: American College of Rheumatology, HAQ-DI: Health Assessment Questionnaire without Disability Index, MTX: methotrexate, NR: not reported

*p <0.001.

†p<0.05 vs. placebo.

Table 3.3. NMA-Derived Proportions of Patients in Each ACR Response Category for JAK Inhibitors and Comparators in TIM Naïve/Mixed Patients at 12 Weeks/Three Months

Treatment	ACR <20	ACR 20-50	ACR 50-70	ACR 70-100
Upadacitinib + cDMARD	33.4%	28.7%	12.8%	25.0%
Tofacitinib + cDMARD	40.5%	28.6%	11.5%	19.4%
Adalimumab+ cDMARD	41.1%	28.5%	11.4%	19.0%
Placebo + cDMARD	72.9%	18.2%	4.5%	4.3%

ACR: American College of Rheumatology, cDMARD: conventional disease-modifying antirheumatic drug

Head-to-Head Studies of JAK Inhibitors in TIM-Naïve/Mixed Populations

There were no head-to-head studies of the JAK inhibitors. However, there were head-to-head studies of the JAK inhibitors and adalimumab in the TIM-naïve/mixed population (Tables 3.1 and 3.2 above).

JAK Inhibitors: Upadacitinib versus Adalimumab

In one head-to-head trial, upadacitinib combination therapy was superior to adalimumab combination therapy in rates of disease remission, ACR response, change in pain, and improvement in HAQ-DI after 12 weeks of follow-up. In general, differences observed at 12 weeks were preserved at 24 and 48 weeks of follow-up, although some drug switching occurred between weeks 14 and 24, so randomization was not fully preserved.

We identified one head-to-head study that compared upadacitinib plus methotrexate with adalimumab plus methotrexate conducted in a primarily TIM-naïve population.[39]

Disease Activity and Remission

There were statistically significant differences observed in the proportion of patients achieving DAS28-CRP clinical remission (<2.6) between combination therapy with upadacitinib plus methotrexate versus adalimumab plus methotrexate (29% vs. 18%, p <0.001), as well as DAS28-CRP <3.2 (45% vs. 29%) and CDAI ≤2.6 (13% vs. 8%).[39]

ACR20/50/70

Relative to adalimumab combination therapy, upadacitinib plus methotrexate showed statistical differences at the ACR20 level (71% achieved ACR20 with upadacitinib vs. 63% with adalimumab; p≤0.05), ACR50 (45% vs. 29%, p<0.001) and ACR70 (25% vs. 13%, p<0.001) at 12 weeks of follow-up.[39] These differences were preserved at 26 and 48 weeks of follow-up.

Radiographic Progression

The rate of no radiographic progression was similar for upadacitinib (86%) and adalimumab (88%, p=NS) at 48 weeks.

HAQ-DI

In the trial comparing upadacitinib combination therapy with TNF inhibitor adalimumab combination therapy, there was a statistically significant difference observed between the mean HAQ-DI change from baseline at 12 weeks in the two groups (-0.60 vs. -0.49, p<0.01).[39]

Other Patient-Reported Outcomes

After 12 weeks of follow-up, patients randomized to upadacitinib experienced greater improvements in quality of life, pain, and fatigue than those randomized to adalimumab therapy.[39]

JAK Inhibitors: Tofacitinib versus Adalimumab

In one head-to-head trial, tofacitinib combination therapy was not statistically different from adalimumab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI after six months of follow-up.

We identified two head-to-head studies that compared tofacitinib plus methotrexate with adalimumab plus methotrexate conducted in a mostly TIM-naïve population.[43,45] The results of the studies are summarized below.

Disease Activity and Remission

There was no statistically significant difference observed in the proportion of patients achieving DAS28-ESR clinical remission or low disease activity between combination therapy with tofacitinib plus methotrexate versus adalimumab plus methotrexate.[43,45]

ACR20/50/70

Relative to adalimumab combination therapy, tofacitinib plus methotrexate showed statistical differences only at the ACR70 level (20% achieved ACR70 with tofacitinib vs. 10% with adalimumab; p≤0.01) at 24 weeks of follow-up in ORAL Standard,[45] but not in ORAL Strategy (25% vs. 21%) at six months.[43]

Radiographic Progression

We did not identify any studies of tofacitinib in comparison to another TIM that reported on radiographic progression.

HAQ-DI

In the trials comparing tofacitinib combination therapy with TNF inhibitor adalimumab combination therapy, there were no statistically significant differences observed between the mean HAQ-DI change from baseline at 24 weeks or one year between the two groups.[43,45]

Other Patient-Reported Outcomes

After 12 weeks of follow-up, patients experienced comparable improvement in quality of life, pain, and fatigue with combination tofacitinib or adalimumab therapy.[46]

JAK Inhibitors: Baricitinib versus Adalimumab

We identified one head-to-head trial that compared baricitinib plus methotrexate to adalimumab plus methotrexate in mostly TIM-naïve patients.[47] However, this trial used a dose of baricitinib that was not approved by the FDA (4 mg instead of 2 mg), so the trial was excluded.

TIM-Experienced Population

Studies for all three JAK inhibitors demonstrated statistically and clinically significant improvements in measures of disease activity, ACR response and HAQ improvement versus conventional DMARDs alone, but there were fewer trials with fewer participants, so the confidence intervals are wider than those for the JAK inhibitors in the TIM-naïve population.

RCT evidence was more limited in patients with inadequate response to one or more TIMs. A total of three randomized trials were identified plus the pooled study of tofacitinib randomized trials. All of the trials studied combination therapy with conventional DMARDs versus conventional DMARDs alone (see Tables 3.4 and 3.5 below). There was one RCT for each of the three JAK inhibitors. The evidence was similar for all three: significantly greater proportions of patients randomized to the JAK inhibitors plus conventional DMARDs achieved low disease activity and remission at three and six months by multiple measures of disease activity (Appendix D) compared with conventional DMARDs alone. They also had greater proportions of patients meeting the ACR20/50/70 response levels and greater improvements in the HAQ-DI compared with conventional DMARDs alone (Table 3.2).

Table 3.4. Disease Activity Outcomes of JAK Inhibitors and Comparators in TIM-Experienced Patients at 12 Weeks/Three Months

Treatment	N	DAS28-ESR or CRP	DAS28 Change from Baseline (Mean)	DAS28 Low Disease Activity (%)	DAS28 Remission (%)	CDAI Low Disease Activity (%)	SDAI Low Disease Activity (%)
SELECT-BEYOND[48]							
Upadacitinib + MTX	164	DAS28-CRP	NR	43*	NR	32*	34*
Placebo + MTX	169	DAS28-CRP	NR	14	NR	14	14
ORAL Step[49]							
Tofacitinib + MTX	133	DAS28-CRP DAS28-ESR	NR -1.8*	13 14.3†	6 6.7†	NR NR	NR NR
Placebo + MTX	159	DAS28-CRP DAS28-ESR	NR -0.7	4 5	1 1.7	NR NR	NR NR
Pooled Tofacitinib Trials[38]							
Tofacitinib + MTX	258	DAS28-ESR	NR	12.7†	6.6†	29.5*	29.8*
Placebo + MTX	191	DAS28-ESR	NR	5.1	2.3	14.4	13.8
RA-BEACON[50]							
Baricitinib + MTX	174	DAS28-CRP DAS28-ESR	-1.5*	24* 13‡	11† 6‡	24‡	22*
Placebo + MTX	176	DAS28-CRP DAS28-ESR	-0.7	9 4	4 1	11	9

CDAI: Clinical Disease Activity Index, CRP: C-reactive protein, DAS28: Disease Activity Score 28, ESR: erythrocyte sedimentation rate, MTX: methotrexate, NR: not reported, SDAI: Simplified Disease Activity Index

*p <0.001.

†p<0.05 vs. placebo.

‡p<0.01.

Table 3.5. ACR20/50/70 and HAQ-DI Outcomes of JAK Inhibitors and Comparators in TIM-Experienced Patients at 12 Weeks/Three Months

Treatment	N	ACR20 (%)	ACR50 (%)	ACR70 (%)	Change in HAQ-DI	HAQ-DI Improved ≥0.22 (%)
SELECT-BEYOND[48]						
Upadacitinib + MTX	164	65*	34*	12†	-0.41*	NR
Placebo + MTX	169	28	12	7	-0.16	NR
ORAL Step[49]						
Tofacitinib + MTX	133	41.7†	26.5*	13.6†	-0.43*	54.2†
Placebo + MTX	159	24.4	8.4	1.5	-0.18	40.5
Pooled Tofacitinib Trials[38]						
Tofacitinib + MTX	258	43.4*	24.4*	9.7†	NR	45.7
Placebo + MTX	191	24.6	10.5	3.1	NR	36.9
RA-BEACON[50]						
Baricitinib + MTX	174	49‡	20‡	13‡	-0.37*	59‡
Placebo + MTX	176	27	8	2	-0.18	43

ACR: American College of Rheumatology, HAQ-DI: Health Assessment Questionnaire without Disability Index, MTX: methotrexate

*p <0.001.

†p<0.05 vs. placebo.

‡p<0.01.

Harms

Rates of short-term serious adverse events (within six months) were generally comparable across all treatments, including JAK inhibitors, adalimumab, and conventional DMARD therapy. Infections (e.g., upper respiratory tract infection, bronchitis, nasopharyngitis) were the most common adverse events during treatment. Based on long-term (one year or more) trial data, upadacitinib, tofacitinib, and baricitinib showed comparable overall safety profiles.

Data on adverse events, discontinuations due to adverse events, as well as specific adverse events of interest observed in clinical trials with conventional DMARD controls are presented as weighted averages (i.e., according to total sample size across trials) in Table 3.6. Of note, these represent events as recorded before treatment-arm crossover was permitted. Most adverse events were of mild-to-moderate severity. The most frequently reported adverse events were mild infections (upper respiratory tract infection, bronchitis, nasopharyngitis). The overall incidence of serious infections, deaths, and all serious adverse events was comparable among treatments, including conventional DMARD therapy. As noted in Table 3.6, however, adverse-event rates for tofacitinib were calculated over a 12-week pre-crossover period, versus 24-28 weeks for the other TIMs.

All three JAK inhibitors carry black-box warnings for serious infections, lymphoma, testing for latent tuberculosis prior to initiating therapy, and monitoring for active tuberculosis. In addition, baricitinib and upadacitinib carry black box warnings regarding thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.

The rates of serious infection, serious adverse events, and discontinuation due to adverse events were generally comparable in the head-to-head trials comparing the JAK inhibitors with adalimumab (see Appendix D, Tables D15-16). There was no evidence of material differences in the rates of malignancies or death between treatment groups across trials.

A systematic review and meta-analysis of 21 RCTs of JAK inhibitors including 11,144 patients looked specifically at rates of serious infections and herpes zoster.[51] They found that the absolute risk for serious infections (hospitalization, death, intravenous antibiotics) was low and was not significantly higher when compared to the placebo group. Similarly, there was an increase in rates of herpes zoster infections, but the increase was not statistically significant.

Table 3.6. Adverse Events During the Conventional DMARD Controlled Period

Estimate (%)*	TIMs Plus cDMARD				cDMARD Plus Placebo
	TOF	BAR	UPA	ADA	
Total (N)†	388	229	221	780	4,683
Any AE	57.3	56.4	56.1	77.3	64.5
Serious AEs	3.9	2	4.4	4.2	5.5
D/C Due to AEs	4.0	3.4	8.3	2.9	2.7
Any Infection	0.5	9.4	1.4	41.9	29.5
Serious Infection	0.5	1.4	1.4	0.9	1.5
TB	NR	0	0	0.5	0
Malignancy	NR	0	0.4	0.3	0.4
Death	0.4	0	0	0.2	0.2

ADA: adalimumab, AE: adverse event, BAR: baricitinib, D/C: discontinuation, cDMARD: conventional disease-modifying antirheumatic drug, TB: tuberculosis, TOF: tofacitinib, UPA: upadacitinib
Note: Serious AEs include specific listed events (e.g., serious infection, malignancy) as well as other events deemed life-threatening or requiring hospitalization by study investigators.
*Values are weighted averages of the percentage of patients with events across key trials.
†Maximum contributing to the weighted average; not every study contributes to all AEs, therefore, N contributing may be less in some AEs.

Observational Study

In a prospective cohort study analyzing data from the Dutch RA monitoring (DREAM) registry, patients with RA who have had prior treatment with at least two conventional DMARDs including methotrexate, starting their first TNF inhibitor (adalimumab, infliximab, or etanercept), were followed for up to five years.[52]

The unadjusted incidence rate of a first serious infection per 100 patient-years was 2.61 (95% CI 2.21 to 3.00) for adalimumab, 3.86 (95% CI 3.33 to 4.40) for infliximab, and 1.66 (95% CI 1.09 to 2.23) for etanercept. Age, year of starting anti-TNF therapy, comorbidities at baseline, and DAS28 score over time were included as confounders. No difference in risk for serious infections was found between adalimumab and infliximab (adjusted HR: 0.90 [95% CI 0.55 to 1.48]), but the risk of serious infections was significantly lower for etanercept than both infliximab (adjusted HR=0.49 [95% CI 0.29 to 0.83]) and adalimumab (adjusted HR=0.55 [95% CI 0.44 to 0.67]).[52] No data were presented for the JAK inhibitors.

Controversies and Uncertainties

Across the RCTs identified for this review, only three were based on head-to-head comparisons of the TIMs of interest and none were head-to-head comparisons of the JAK inhibitors. The paucity of trial data and the differences in reported measures of disease activity at three months precluded using an NMA to combine direct and indirect evidence of efficacy. Often the studies reported outcome measures at six months even though patients were eligible for rescue therapy and/or treatment-arm crossover 12-24 weeks after randomization. Since guidelines increasingly recommend treatment-switch decisions within three months of initiating therapy, the three-month outcomes would have been both more clinically relevant and methodologically more rigorous.

Extending trial-based analyses to longer timepoints requires imputation in many instances, which affects the level of confidence in the results no matter how responsibly it is done. In addition, key outcome measures such as disease activity scores, remission criteria, and modified Sharp score have undergone substantial revision and modification over the years, are employed variably in clinical trials, and not measured in others, making cross-trial comparisons problematic.

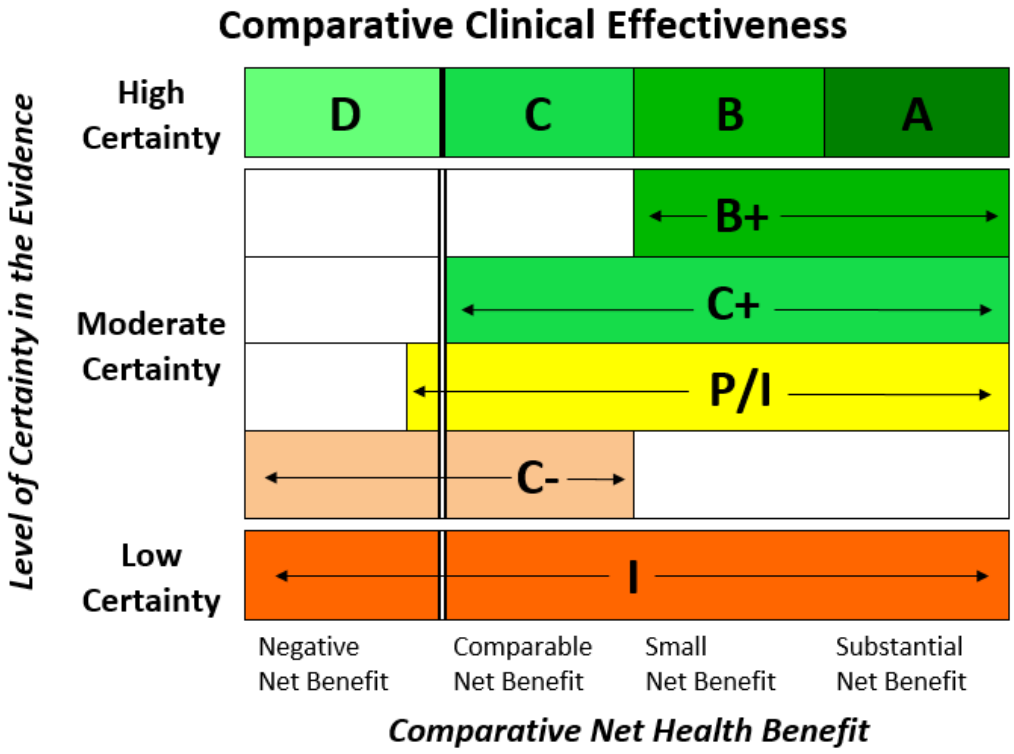
The course of RA may feature multiple periods of remission and flares of symptoms due to the complex and heterogeneous nature of the disease. TIM therapies are chronic, and the long-term effects of prolonged immunomodulation—both clinical benefits and potential harms—are not well-understood for all therapies, particularly for newer classes of TIMs. Evidence is beginning to emerge on the question of whether TIM doses can be modulated or therapy suspended in patients with evidence of durable remission, but early results are limited and mixed. In addition, as noted in Section 1 of this report, some patients may be started on TIM treatment prior to optimization of conventional DMARD therapy[53]; such challenges are common to other chronic diseases such as diabetes and heart failure as well.

Finally, while the introduction of TIMs has transformed clinical practice in RA and improved the quality of life and functional capacity of many patients, there are still unanswered questions, including the relationship between levels of disease activity and radiographic evidence of joint damage, whether there are patient or clinical factors that predict response to specific therapies, and the totality of the disease's impact on patients, families, and caregivers. As noted in Section 1

of this report, patient groups do not feel that the current tools for patient-reported outcomes sufficiently capture their experience, but to date no new instruments have been accepted into common use in clinical trials.

3.4 Summary and Comment

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Using the ICER Evidence Rating Matrix, our evidence ratings for selected comparisons of interest are provided in Table 3.7 for patients with moderately-to-severely active RA who have had an inadequate response to prior conventional DMARD therapy and are TIM-naïve. As described previously, findings of studies using conventional DMARDs as the control indicate clinically and statistically significant improvements in most important disease measures for upadacitinib and tofacitinib combination therapy, so both receive a letter grade of "A" (high certainty of substantial

net health benefit) relative to conventional DMARD therapy alone. However, there is a paucity of evidence on baricitinib 2 mg daily in this population and it does not have an FDA indication for this population, so we judge the comparative clinical effectiveness of baricitinib to be insufficient ("I").

Table 3.7. Evidence Ratings for Comparative Clinical Effectiveness: Selected Comparisons

Regimen Type/Comparison	Intervention	Comparator	Rating
TIM-Naïve Population			
Compared to cDMARD	Upadacitinib	cDMARDs	A
	Tofacitinib	cDMARDs	A
	Baricitinib	cDMARDs	I
Head-to-Head	Upadacitinib	Adalimumab	B+
	Tofacitinib	Adalimumab	C+
	Baricitinib	Adalimumab	I
TIM-Experienced Population			
Combination with cDMARD	Upadacitinib	cDMARDs	B+
	Tofacitinib	cDMARDs	B+
	Baricitinib	cDMARDs	B+

cDMARD: conventional disease-modifying antirheumatic drug, TIM: targeted immune modulator

Single RCTs have also evaluated combination therapy regimens of both upadacitinib and tofacitinib plus conventional DMARDs in head-to-head comparison with adalimumab plus conventional DMARDs in the TIM-naïve population. In the SELECT-COMPARE study, upadacitinib plus methotrexate was associated with statistically-significantly but modestly higher rates of disease remission, ACR response, change in pain, and improvement in HAQ-DI. The difference in benefits was smaller than those seen in comparison to conventional DMARDs alone. Rates of serious harm or discontinuation due to adverse events were also similar, so we judge the evidence for combination therapy with upadacitinib versus adalimumab to represent an incremental or better net health benefit ("B+"). There were no significant differences in clinical outcomes between combination regimes using tofacitinib versus adalimumab in two trials, although there was a trend towards more patients randomized to tofacitinib achieving ACR70 and having greater improvements in the HAQ-DI. We therefore assign a net health benefit rating of comparable or better ("C+") for this comparison. Finally, there is no evidence on baricitinib 2 mg daily versus adalimumab in this population, so we judge the comparative clinical effectiveness of baricitinib to be insufficient ("I").

For each of the JAK inhibitors, there is one randomized trial comparing combination therapy to conventional DMARDs in the TIM-experienced population. All three trials are smaller than those for the TIM-naïve population and the effect sizes are also somewhat smaller with wider confidence intervals. As in the TIM-naïve population, rates of serious harms and discontinuation due to adverse events were low, so we judge the evidence for combination therapy with each of the three

JAK inhibitors versus conventional DMARDs alone to represent an incremental or better net health benefit ("B+").

There is much greater uncertainty in assessing the relative comparative clinical effectiveness of the JAK inhibitors, which have never been compared head-to-head in a randomized setting. The individual clinical trials had somewhat different patient populations, primary endpoints, timing of assessments, and timing of allowable switching to alternative therapies. As a result, we judge there to be insufficient evidence ("I") to differentiate among the JAK inhibitors.

Biosimilars for RA

A biosimilar is a biologic drug that is highly similar in structure and function to a licensed reference product. In contrast to a generic (which is a small molecule that can be predictably duplicated), a biosimilar is a larger and more complex molecule that can be sensitive to changes in the manufacturing process. The FDA requires that manufacturers demonstrate that there is no clinically meaningful differences in safety, purity, and potency between the biosimilar and the reference product.[54] The Biologics Price Competition and Innovation Act (BPCI) of 2009 created an abbreviated licensure pathway for products shown to be biosimilar to or interchangeable with an FDA licensed reference product.[55] In Europe, the European Medicines Agency requires that the two products show evidence of similarity in quality, safety, and efficacy.

The FDA approval pathways for biologics and for biosimilars are different. Under the Public Health Service Act, the standard pathway for approval of biologics is described in Section 351 (A). The application requires all the information regarding safety and effectiveness of a biologic product. It is considered a standalone application and does not depend on any other drug or biologic. Approval via the 351 (K) pathway is for biosimilars. This application is submitted for approval to receive FDA designation as a biosimilar or the more stringent interchangeable designation. The proposed biosimilar must have the same mechanism of action for the intended condition(s) of use. The route of administration, dose form, and strength must be the same as that of the reference product. Applications are also required to provide details about product manufacturing to ensure safety and efficiency of manufacturing plant and process. Of note, once a biosimilar has been approved, it may be prescribed for any indication allowed for the reference product, even if the biosimilar has not been studied in that patient population.[56] … biosimilars may be approved for indications for which the reference product has been approved, through the process of extrapolation.[56]

Interchangeability as defined for a biologic product means that the biologic product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.[56] The standards for designation as "interchangeable" include those required to be approved as a biosimilar. In addition, manufacturers must demonstrate that

the safety and efficacy of therapy alternating or switching between the interchangeable agent or the reference product is non-inferior to continuing the reference product without switching.

Biosimilar naming follows a standard approach. Each nonproprietary name for a biological product includes the reference product name followed by a hyphen and a four-letter suffix. For example, the biosimilar example used in this report is infliximab-dyyb. The reference biologic for infliximab-dyyb is infliximab.[57]

As implied by its name, the Biologics Price Competition and Innovation Act was intended to increase competition in the marketplace and decrease cost, analogous to what occurred when generic drug legislation was passed. Although more than 20 biosimilars have been approved, significant cost reductions have not been observed in the US and the uptake of biosimilars has been modest. No biologics have yet been approved as "interchangeable."

Infliximab Biosimilar (Inflectra/CT-P13/Infliximab-dyyb, Pfizer)

The PLANETRA (Programme evaluating the autoimmune disease investigational drug CT-P13 in RA patients) trial randomized patients with RA to infliximab-dyyb or to its reference biologic infliximab. The investigators randomized 606 patients (83% female) with active RA and an inadequate response to methotrexate.[58] The primary endpoint was ACR criteria for ≥20% clinical improvement response (ACR20) at 54 weeks. Additional endpoints included ACR50, ACR70, DAS28-ESR, and DAS28-CRP, SDAI, CDAI, the percentage of patients with response defined according to EULAR criteria, patient-reported outcomes, joint damage progression, safety endpoints and laboratory abnormalities, and immunogenicity endpoints.

A total of 455 of the 606 patients were treated up to week 54. At 54 weeks, there was no difference between groups who met the primary endpoint (74.7% biosimilar vs. 71.3% reference). The proportion of patients achieving ACR50 and ACR70 at 54 weeks was also comparable between groups.

DAS28-ESR, DAS28-CRP, SDAI, and CDAI scores were similar between groups at 54 weeks follow up. Mean decreases in baseline of DAS28-ESR, DAS28-CRP, SDAI, and CDAI were 2.4, 2.3, 26.3, and 25.7 compared with 2.4, 2.2, 24.6, and 24.0 for the reference product. The proportion of patients with good and moderate EULAR response to treatment was similar between the two groups. With respect to patient-reported outcomes, the VAS for patient assessment of pain showed similar reductions from baseline in both groups (30.2 vs. 28.4 at week 54). There were no differences in the immunologic outcomes, including the development of anti-drug antibodies.

Treatment-related adverse events were similar between groups (70.5% vs. 70.3% in the reference product). Twenty-two patients (7.3%) in the infliximab-dyyb group had latent tuberculosis compared with 20 (6.7%) in the reference product group. There were no cases of active tuberculosis or lymphoma at 54-week follow-up in either group.

To assess whether the biosimilar is interchangeable with the reference product, studies that compare switching from the reference product to the biosimilar versus continuing on the biosimilar are required. In an extension of the PLANETRA study, 305 of the 455 patients who completed the study enrolled into the extension study.[59] The switch group from the reference product to infliximab-dyyb was compared to the maintenance group continuing infliximab-dyyb after an additional 48 weeks follow-up. The primary outcomes were ACR20, ACR50, and ACR70 at week 102. Response rates for maintenance versus switch groups were 71.7% versus 71.8% for ACR20, 48.0 % versus 51.4% for ACR50, and 24.3% versus 26.1% for ACR70. There were no differences in other efficacy endpoints including DAS28 score changes and EULAR response criteria. Similar proportions of patients reported treatment-related adverse events in the two groups (53.5% vs. 53.8%). Rates of serious adverse events were similar in the maintenance and the switch groups (7.5% vs. 9.1%). Rates of latent tuberculosis were similar to those seen during the main trial and there were no cases of lymphoma.

Finally, in an observational study conducted in Bulgaria, 151 patients with severely active RA (n=81) or ankylosing spondylitis (n=70) were treated with infliximab-dyyb for 24 weeks.[60] The primary outcome for patients with RA was the DAS28-CRP score. Patients with RA had a significant reduction in DAS28-CRP score when compared to baseline. A total of 4.8% of participants reported an adverse event. Two out of seven serious adverse events were considered possibly treatment related. There were no cases of lymphoma or active tuberculosis. CT-P13 was relatively safe and effective.

Infliximab-dyyb was approved as a biosimilar by the FDA, but it has not yet been approved as interchangeable. Since interchangeability designates whether products can be substituted by a pharmacist, it is uncertain whether products distributed through infusion centers will seek this designation. The FDA draft guidance on interchangeability was published in January 2017. The guidance was finalized in May 2019.

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis is to estimate the cost effectiveness of JAK inhibitors for patients with moderately-to-severely active RA using a decision analytic model. The model's objective was to compare each of the three JAK inhibitors, upadacitinib, baricitinib, and tofacitinib, to adalimumab, a TNF inhibitor. Since the publication of our modeling analysis plan and the presentation of preliminary modeling methods on August 5, 2019, we have modified our objective to answer the policy-relevant question of the value of the JAK inhibitors indicated for first line TIM use after failure of a conventional DMARD, relative to adalimumab, which is currently used most commonly as first line TIM treatment following conventional DMARD failure. However, we were unable to draw a comparison between tofacitinib and adalimumab due to inadequate data in the targeted immunomodulator (TIM)-naïve or TIM-experienced population, and between upadacitinib and adalimumab in the TIM-experienced population. Given the labeled indication for baricitinib—use in a population in whom treatment with a TNF inhibitor has failed—we attempted to compare it to adalimumab in the TIM-experienced population but were unable to do so due to a lack of comparable data.

In all analyses, the JAK inhibitors and adalimumab will be considered as add-on therapies to conventional DMARD therapy in the TIM treatment arms. In the base-case analysis and in scenario analyses, unless otherwise specified, the JAK inhibitors and adalimumab will be considered as add-on therapies to conventional DMARD therapy in the TIM treatment arms. The base-case analysis takes a health care sector perspective (i.e., focus on direct medical care costs only) and a lifetime time horizon. Productivity losses were considered in a scenario analysis. The model was developed in hēRo3℠, with some components of the model, such as survival distributions, developed in RStudio (Version 1.1.463).

hēRo3 is a Web-based, health economic modeling platform that supports the development of both Markov cohort and partitioned survival models (Policy Analysis Inc., Brookline, MA). Calculations in hēRo3 are performed in the programming language, R, using an open-source health-economics modeling package, called "heRomod" (https://github.com/PolicyAnalysisInc/heRomod), that runs in a secure virtual private cloud. heRomod is a modified version of the open-source, health-economics modeling package, HEEMOD (http://cran.r-project.org/package=heemod). An extensive set of unit tests is available to validate calculations of the modeling package. Further details on hēRo3 are available in Appendix E.

4.2 Methods

Model Structure

We developed a *de novo* decision-analytic model for this evaluation, informed by key clinical trials and prior relevant economic models. While this model was informed by the model developed for ICER's 2017 RA review, there were several changes made to accommodate recommendations that attempt to reflect current clinical practice in RA and simultaneously isolate the true health and economic benefit of the treatment strategies included. Costs and outcomes in this model were discounted at 3% per year.

The primary model focused on an intention-to-treat and treat-to-target analysis, with a hypothetical cohort of patients with severe RA for whom prior treatment with conventional DMARDs has failed. Upon model entry, the hypothetical patient cohort was initiated on a treatment strategy, with treatment response assessed at three months. In all analyses, a TIM was added to a conventional DMARD, such as methotrexate. Treatment switching was based on disease activity as measured by the DAS28-CRP value (Table 4.1), with those in remission and with low disease activity remaining on the same treatment after the first three months, while those with moderate/high disease activity switching to a subsequent line of therapy at the end of the first three-month cycle.

Table 4.1. Disease Activity Based on DAS28 Categories

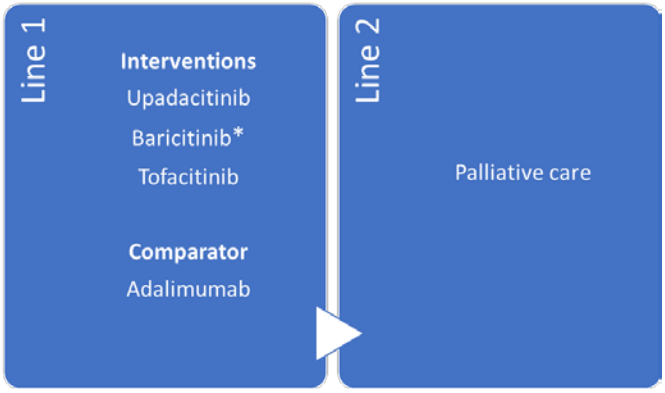
DAS28	Disease Activity
<2.6	Remission
2.6 to ≤3.2	LDA
>3.2 to ≤5.1	MDA
>5.1	HDA

DAS28: Disease Activity Score 28, , LDA: low disease activity, MDA: moderate disease activity, HDA: high disease activity
Source: Canhão et al., 2018[61]

In a real-world clinical setting, it is not uncommon for patients to cycle through multiple therapies before finding a treatment option that they best respond to and tolerate. However, there is a lack of guidelines or published real-world evidence to standardize treatment sequencing for RA patients. In addition, the purpose of this analysis is to determine the cost effectiveness of specific treatments and not treatment sequences. Thus, treatment switching was assumed to be to palliative care. We chose palliative care in order to isolate the health and economic benefits of the first line TIMs. Once in palliative care, patients could not transition to remission or low disease activity. After the first three months on first line treatment those with moderate/high disease activity switched to palliative care, while those in remission/low disease activity stayed on treatment, switching to palliative care over time from discontinuation of first line TIMs for reasons such as loss of efficacy,

adverse events, patient and clinician preferences, and access restrictions. In order to best compare the relative cost effectiveness of specific products and not the cost effectiveness of different treatment sequences, we standardized treatment sequence beyond first line TIMs.

Figure 4.1. RA Treatment Sequence



*Only in a scenario analysis for a TIM-experienced population.

After initiating treatment with a TIM, the model relates the DAS28-based response to the HAQ after three months of therapy. Other previously published models, including the previous 2017 ICER RA Model, mapped the ACR response or the EULAR to the HAQ after six months of therapy.[62-64] Our model uses a three-month cycle length because we understood from clinicians that this more closely aligns with the timepoint that clinicians currently use in the recommended treat-to-target approach.[6]

A DAS28-to-HAQ mapping would ideally model hospitalization and outcomes such as quality of life and productivity loss, which were modeled as dependent on the HAQ. We found one other published model that related the DAS28 to HAQ score, but at six months of therapy.[65] We found clinical trial data on the proportions of patients within different categories of disease activity based on the DAS28 at three months for all treatments included in line one, but did not find a robust DAS28-to-HAQ mapping algorithm at three or six months for all treatment strategies included. We hence used a mapping algorithm from EULAR to HAQ (Table 4.2). The EULAR response is divided into three response categories: "Good," "Moderate," and "None," and is based on the baseline DAS28 and the change in DAS28 from baseline at the timepoint measured. Here, we assumed remission as defined by DAS28 as equivalent to "Good" response, low disease activity as equivalent to "Moderate" response, and moderate disease activity and high disease activity as equivalent to "None" on the EULAR scale. While the HAQ-to-EULAR response mapping indicates HAQ change at six months, we assumed this to be the same at three months, which likely overestimates the benefit and biases the results in favor of the TIMs.

Table 4.2. Relationship Between EULAR and HAQ

EULAR Response	Mean HAQ Change	Standard Error
Good	-0.672	0.112
Moderate	-0.317	0.048
None	0	0

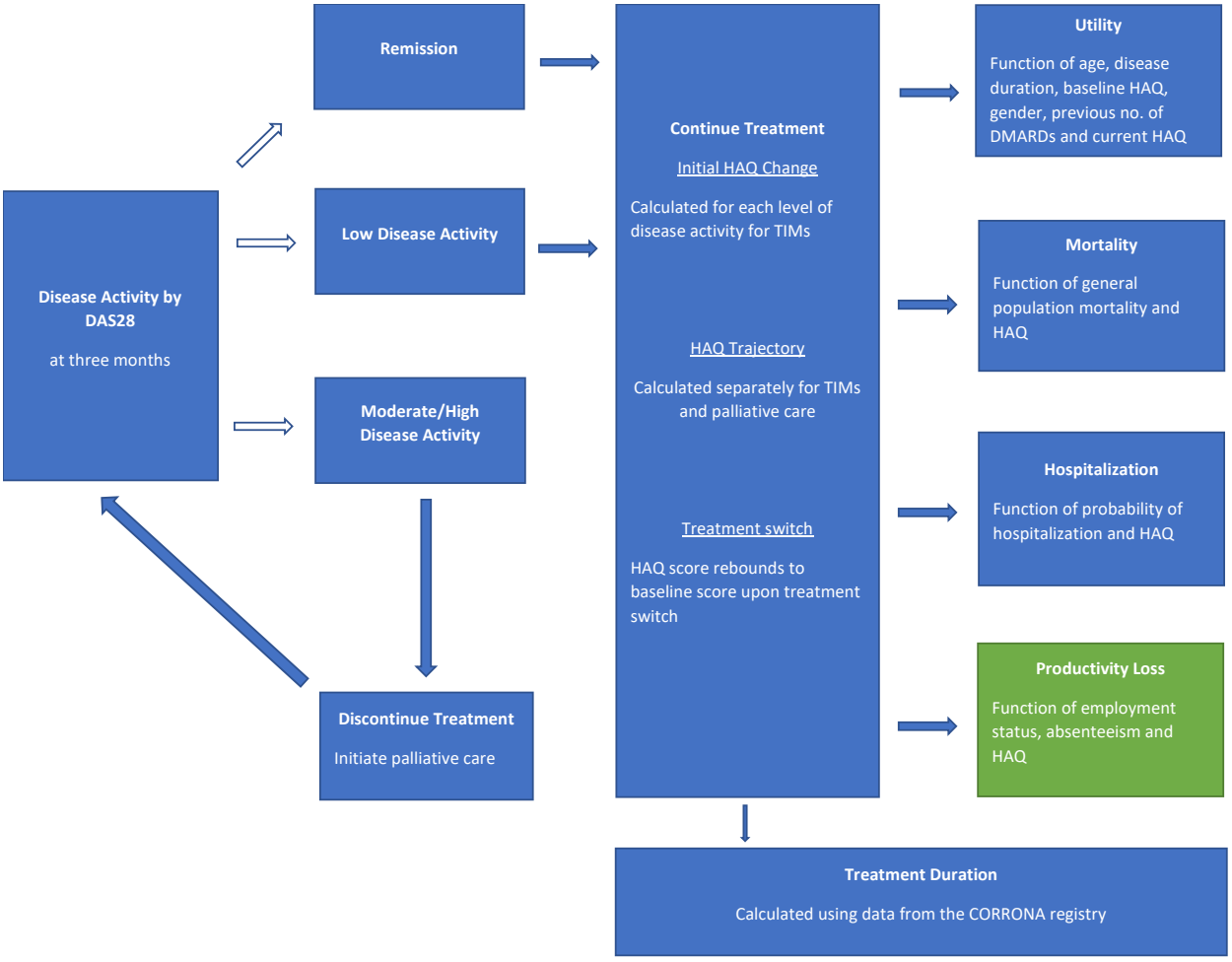
EULAR: European League Against Rheumatism, HAQ: Health Assessment Questionnaire
HAQ change mapping to EULAR response categories was estimated from the British Society for Rheumatology Biologics Register and has been used in the other published economic evaluations.[63]

The HAQ score was then linked to utility, mortality, hospitalizations, and productivity. Simulated utility scores and mortality were used to calculate the quality-adjusted life years (QALYs) gained, with hospitalization costs and productivity loss costs contributing to the health care sector perspective and societal perspective analyses, respectively (Figure 4.2). Long-term HAQ scores were simulated until treatment discontinuation or death, with relevant estimates for long-term HAQ changes applied to those on TIMs and palliative care.

Patients remained in the model until death. All patients were allowed to transition to death from all causes and from RA-related mortality.

Modeled outcomes include lifetime costs, life years (LYs), QALYs, and equal value of life years gained (evLYG). An analysis of the incremental cost per evLYG is included in this report to complement the cost per QALY calculations and provide policymakers with a broader view of cost effectiveness. A description of the methodology used to derive the evLYG can be found in Appendix E. Additionally, we measured the duration in remission when on line one TIM treatment and the incremental cost of remission when on line one TIM treatment.

Figure 4.2. Model Schematic



DMARD: disease-modifying antirheumatic drug, DAS28: Disease Activity Score 28, HAQ: Health Assessment Questionnaire, TIM: targeted immune modulator
Productivity losses will be measured in the modified societal perspective scenario analysis.

Target Population

The primary population of focus for the economic evaluation included adults in the US with severely active RA with inadequate response to conventional DMARDs. The model simulates a hypothetical homogeneous cohort of patients with baseline characteristics consistent with severely active RA similar to those seen in the key trials for all first line TIM therapies. Because most of these trials had patients with similar baseline characteristics, we used those from the SELECT-COMPARE trial in our modeled population for the base-case analysis, as it included two of the three TIMs assessed in this review.[39] While TIMs are indicated across populations with all levels of disease activity, we chose to model patients with only severely active RA to match the population from the key clinical trials included in this review.

Table 4.3. Baseline Population Characteristics

	Mean Value	Source
Age	54 years	SELECT-COMPARE[39]
Female (%)	79%	
RA Duration	8 years	
Baseline HAQ	1.6	
Baseline DAS28	5.8	

DAS28: Disease Activity Score 28, HAQ: Health Assessment Questionnaire, RA: rheumatoid arthritis

Treatment Strategies

The list of interventions included in this cost-effectiveness review followed the same PICOTS criteria used for the clinical review and was developed with input from stakeholders. The full list of interventions is as follows:

- Upadacitinib
- Baricitinib
- Tofacitinib

Although there exists clinical trial data on the efficacy of baricitinib in the TIM-naïve population, it is currently approved for use only in the TNF inhibitor-experienced population. Its cost effectiveness was not analyzed in the TIM-experienced population owing to lack of comparable data to adalimumab.

Comparators

- Adalimumab

In all analyses, the TIMs were considered add-on therapies to conventional DMARDs versus conventional DMARD therapy alone. Due to a lack of data allowing for a comparison of tofacitinib to adalimumab (head-to-head or through an NMA), we were able to comment on tofacitinib's value relative to adalimumab only via its comparison to conventional DMARDs. This is detailed in Section 4.3. The efficacy of conventional DMARDs in this case was trial- and intervention-specific, with estimates for adalimumab derived from the upadacitinib trials (SELECT-COMPARE), and for tofacitinib from the tofacitinib trial.[38,39]

Key Model Characteristics and Assumptions

Our model includes several assumptions, stated below.

Table 4.4. Modeling Assumptions

Assumption	Rationale
A treat-to-target approach was used, with treatment switching dependent on disease activity as measured by DAS28.	We used a treat-to-target approach to align with real-world clinical practice, using DAS28 to assess the likelihood of treatment switching.
A three-month cycle length has been adopted, rather than the commonly used six-month cycle length seen in several previously published RA economic models,[62,63,65] including the model developed for the 2017 ICER RA Review.	The three-month cycle length more closely aligns with the average length of time clinicians wait before assessing the need for treatment switching using a treat-to-target approach.[6] Additionally, we have clinical trial data on the proportion of patients with different levels of disease activity, as defined by the DAS28, at three months for all treatment strategies included in line one.
We assumed conversion ratios of 2x and 1.5x for DAS28-ESR to DAS28-CRP to derive the proportions in remission and low disease activity for tofacitinib and its conventional DMARD comparator.	Some trials (SELECT-monotherapy, RA-BUILD, RA-BEACON, and ORAL-STEP) simultaneously reported DAS28-ESR and DAS28-CRP outcomes for upadacitinib, baricitinib, and tofacitinib, and their respective comparators. An average of the disease activity proportions using DAS28-CRP and DAS28-ESR data was used to estimate an approximate 2x and 1.5x ratio of DAS28-CRP to DAS28-ESR in the TIM arms, while the conventional DMARD arms showed more variability. In the absence of DAS28-CRP trial data at three months, we applied these ratios to the DAS28-ESR data to derive DAS28-CRP data at three months for tofacitinib and its conventional DMARD comparator. The uncertainty surrounding this will be tested in a sensitivity analysis.
We adopted the EULAR-to-HAQ mapping algorithm for the different DAS28 disease activity categories, assuming remission to reflect "Good" EULAR response, low disease activity to reflect "Moderate" EULAR response, and moderate disease activity and high disease activity to reflect EULAR response of "None."	All trials report DAS28 categories by remission, low disease activity, and a moderate disease activity/high disease activity combination, but we found no robust published evidence mapping DAS28 to HAQ for any included treatment strategies.
No dose increase was assumed for those in the low disease activity category, as measured by the DAS28, at three months after initiation of a new TIM.	Clinical experts indicated that a dose increase for those with low disease activity but not in remission is patient-specific and not necessarily uniformly practiced for all drugs.
At three months after initiation of a new TIM, those with moderate/high disease activity, as measured by	Clinical experts reported that they would most likely initiate a new treatment switch if their patients had

the DAS28, were assumed to switch to palliative care. Similarly, those with low disease activity who later discontinue their first TIM switched to palliative care.	moderate/high disease activity at the time of assessment. While this switch could be to a different TIM, as stated earlier, in order to isolate the effect of first line TIMs, we assumed second line treatment as palliative care.
Upon treatment discontinuation, HAQ rebounds to baseline HAQ.	We are unaware of any robust data on the magnitude of HAQ rebound upon treatment discontinuation. We hence assumed a rebound to baseline HAQ and vary this in the sensitivity analysis.
We assumed the same discontinuation rate among those with remission/low disease activity for all TIMs following the initial three months of therapy.	Prior evaluations attempting class-level economic evaluations have cited errors of confounding in observational studies reporting discontinuation rates. Additionally, because these therapies have been approved over time, there is no consistent comparison of discontinuation rates among treatments.[63,64]
The rate of serious infection is assumed to be the same for all TIMs.	Serious infection measured in the trials does not reflect infection rates beyond the duration of the trials. Real-world estimates of infection rates are difficult to interpret as many patients switch therapies multiple times, which makes a risk attribution to a single therapy difficult. Differences in patient baseline risk for infection further complicates interpretation. In this case, serious infection rates across studies were similar. We therefore chose to use a standardized rate of serious infection across therapies, an approach used in other models.[63-65]
Once in palliative care, we assumed HAQ degradation over time will be 0.0269 per year for the first 15 years in the model, after which it is assumed to flatten with no additional annual degradation. This assumption reflects the HAQ trajectory of conventional DMARDs as undertaken in the model for 2017 ICER RA Review**.**	Findings from the National Databank on Rheumatic Diseases (NDB) show a degradation of HAQ over time among patients not on TIMs.[66] The HAQ degradation over time reduces in magnitude, but not in a linear manner. We hence assumed a flattening of the HAQ after 15 years in the model for patients remaining on conventional DMARD therapy. We altered this HAQ progression using other data estimates from the NDB, as done in a scenario analysis in a prior published economic evaluation.[65,67]
When on TIMs, a long-term HAQ improvement of -0.001 annually was assumed and standardized for all TIMs assessed.	Data from the NDB estimated a long-term improvement in HAQ at -0.001 annually among patients on TIMs.[68]
We assumed no additional cost for palliative care.	We understand there exists no active substantial drug-related treatment costs when in palliative care and we hence assumed no cost. The only costs when in palliative care are those attributed to background monitoring costs, lab costs, and costs of hospitalization, which is a function of the HAQ score.

Model Inputs

Clinical Inputs

Treatment Response

Inputs on the proportion of patients with different levels of disease activity have been derived from individual trials for relevant interventions and comparators (Table 4.5 and Table 4.6). We were unable to draw a comparison between tofacitinib and adalimumab in our analyses due to a lack of comparable efficacy data. Our comparison was therefore restricted to only upadacitinib versus adalimumab. However, we comment on the value of tofacitinib relative to adalimumab based on the relative cost effectiveness of these TIMs when compared to conventional DMARDs in their respective trials. The approach and data used for this has been detailed in Appendix E. For the subsequent line of therapy (i.e., palliative care) we assumed 0% probability of transitioning to remission or low disease activity from moderate/high disease activity. Palliative care in our model was assumed to be non-specific RA treatment.

Table 4.5. Treatment Response at Three Months using DAS28

	Proportion of Patients Achieving Different Categories of Disease Activity by DAS28 at Three Months*		
	<2.6 (Remission)	2.6 to ≤3.2 (LDA)	>3.2 (MDA and HDA)
Upadacitinib + cDMARD	29%	16%	55%
Adalimumab + cDMARD	18%	11%	71%

cDMARD: conventional disease-modifying antirheumatic drug, DAS28: Disease Activity Score 28, LDA: low disease activity, MDA: moderate disease activity, HDA: high disease activity, TIM: targeted immune modulator
*Mutually exclusive categories.

Table 4.6. Treatment Efficacy Estimates for Adalimumab, Tofacitinib, and Their Respective Conventional DMARD Comparators at Three Months

	Proportion of Patients Achieving Different Categories of Disease Activity by DAS28 at Three Months*		
	<2.6 (Remission)	2.6 to ≤3.2 (LDA)	>3.2 (MDA and HDA)
Tofacitinib + cDMARD	15%	14%	71%
Adalimumab + cDMARD	18%	11%	71%
cDMARD†	6%	8%	86%
cDMARD‡	5%	3%	92%

cDMARD: conventional disease-modifying antirheumatic drug, DAS28: Disease Activity Score 28, HDA: high disease activity, LDA: low disease activity, MDA: moderate disease activity
*Mutually exclusive categories.
†Versus adalimumab.
‡Versus tofacitinib.

Discontinuation

Among those treated with TIMs, a proportion of patients in moderate disease activity and high disease activity at three months after initiation of therapy transitioned to palliative care. These proportions were estimated from relevant trial data. Patients in remission and with low disease activity at three months after treatment initiation were assumed to continue on initial therapy. We included estimates of later treatment discontinuation due to other reasons such as loss of efficacy, serious adverse events including infections, and physician and patient preferences based on data from an observational study of RA patients in the CORRONA registry.[69] The study included a sample of over 6,000 adult RA patients treated between 2002 and 2011 receiving TIMs, predominantly TNF inhibitors. While these data are not specific to the JAK inhibitors, we believe they can be generalized in the absence of comparable long-term data for these therapies. We digitized the reported Kaplan-Meier (KM) curves and fit relevant parametric distributions to the curves based on Akaike Information Criteria (AIC), and extrapolated the fitted curves over the modeled time horizon. Because the sampled population in the CORRONA registry comprised of patients with moderate disease activity, we adjusted this curve to represent discontinuation among patients with remission/low disease activity using an odds ratio (OR) of 0.52 as reported by Zhang et al.[70] Following Stevenson et al. and the Innovation Value Initiative (IVI) RA modeling group, we assumed the same long-term discontinuation rate for all TIMs due to issues of bias and confounding found in observational studies for specific TIMs.[63-65]

For conventional DMARDs, following the methods adopted by Stevenson et al. and the IVI RA modeling group, we assumed that those who were on conventional DMARD treatment for at least three months had the same treatment duration as those on TIMs.[63-65] This was done only for the comparison of tofacitinib and adalimumab to their respective conventional DMARD comparators when evaluating the relative value of tofacitinib compared to adalimumab.

Mortality

Gender and age-specific mortality were sourced from the Human Mortality Database's US-specific tables.[71] Prior evidence suggests that improved (lower) HAQ scores are associated with lower likelihood of death and that the HAQ was the most significant predictor of mortality in RA patients.[72] The HAQ calculated at the beginning of each cycle for each health state in the model informed the mortality at the end of the cycle. The quantitative relationship between HAQ and mortality was assumed to be the same as that used in the 2017 ICER RA Review and was based on a published US RA cost-effectiveness study.[62] The mortality equation used was:

US RA-severity specific mortality rate = all-cause mortality*1.33^{HAQ}

Adverse Events

We included only adverse events related to serious infection, aligning with approaches used in prior economic evaluations of RA treatments.[63-65] As stated in Table 4.7, we assumed that the rate of serious infection was uniform across TIMs, as published estimates of serious infection associated with specific TIMs do not represent long-term risk and are likely inaccurately estimated, as mentioned in previously published literature. Estimates on serious infection were sourced from an NMA by Singh et al. (Table 4.7).[73] We assumed the same rate of serious infection with palliative care as with conventional DMARDs. As in the 2017 ICER RA Review and in prior models, we attributed a disutility of 0.156 for a one-month period following a serious infection, along with the relevant costs of treating the infection.

Table 4.7. Adverse Events (Serious Infection)

Parameter	Value (95% CI)*	Source
TIM	0.035 (0.027 – 0.046)	Singh et al., 2011[73]
Palliative Care/cDMARD†	0.026 (0.020 – 0.034)‡	

cDMARD: conventional disease-modifying antirheumatic drug, CI: confidence interval, NR: not reported, TIM: targeted immune modulator

*Calculated as per person-year.

†The cDMARD value was used only for the comparison of tofacitinib and adalimumab to their respective cDMARD comparators when evaluating the relative value of tofacitinib when compared to adalimumab.

‡For the one-way and probabilistic analyses, we assumed upper and lower bounds based on the proportionate variation observed for TIMs.

Health State Utilities

As in the 2017 ICER RA Review, the relationship between HAQ and utility score was based on Wailoo and colleagues' publication.[74] The utility scores from Wailoo and colleagues were based on health state time-tradeoff evaluations made by a US general population sample using the EuroQol (EQ-5D) index, one of the most widely used instruments in health-state valuation.[75] We compared the Wailoo et al. utility change from HAQ score moving from 1.0 to 1.5 to the utility change from a more advanced mathematical model.[76] Although the Wailoo et al. relationship produces a higher utility within the HAQ range of 1.0 to 1.5, the change in utility for this HAQ range was approximately 0.1, consistent with the change in the other model. Uncertainty in the Wailoo et al. mapping will be evaluated in parameter sensitivity analyses. EQ-5D scores were calculated using this equation:

EQ-5D score = 1 – 1/(1+ exp(2.0734 + 0.0058*age + 0.0023*disease duration – 0.2004*baseline HAQ – 0.2914*male + 0.0249*# previous DMARDs – 0.8647*current HAQ))

Additionally, a disutility (-0.156) was assigned for one month to individuals who experienced a serious infection.[63]

Drug Utilization

The inputs used to model drug utilization and associated costs are shown in Table 4.8.

Table 4.8. Treatment Regimen Recommended Dosage

Treatment	Upadacitinib	Baricitinib*	Tofacitinib	Adalimumab	Methotrexate
Brand Name	Rinvoq	Olumiant	Xeljanz	Humira	Generic
Manufacturer	AbbVie	Eli Lilly	Pfizer	AbbVie	Multiple manufacturers
Route of Administration	Oral	Oral	Oral	Subcutaneous injection	Oral
Dosing	15 mg once daily	2 mg once daily	5 mg twice daily†	40 mg every other week	15 mg weekly‡

mg: milligram

*Included only in a scenario analysis comprising a TIM-experienced population.

†Extended release version is dosed at 11 mg once daily.

‡Most patients are on an average dose of 15 mg weekly, although recommended dose is 7.5 mg weekly.

Economic Inputs

Drug costs in the model are current. All other costs were inflated to 2018 values unless otherwise specified.

Drug Acquisition Costs

Drug costs included the cost of acquisition. We obtained net price data from SSR Health[77] that combine information on net US dollar sales with information on unit sales to derive net pricing at the unit level across all payer types. Data on the approved drugs of interest were current through the first quarter of 2019, except for upadacitinib, which was approved on August 16, 2019. We estimated net prices for the TIMs with SSR price data by comparing the four-quarter rolling averages (i.e., second quarter 2018 through first quarter 2019) of both net prices and wholesale acquisition cost (WAC) per unit to arrive at an average discount from WAC for each drug. We then applied this derived discount to the latest WAC[78] of the TIMs of interest. We derived a net price for each TIM using the current WAC and discount from the SSR database.

Because upadacitinib was recently approved for use, we did not find any estimates on its net price in the SSR dataset. Thus, based on the ICER Reference Case, we assumed its WAC to be discounted by 26%, the average discount of the other two JAK inhibitors as seen in the SSR dataset, to estimate its net price.[77] All annual prices presented in Table 4.9 below assume 100% compliance.

For the cost of conventional DMARDs, we use the mean WAC of the multiple generic versions of methotrexate, aligning with the ICER Reference Case. We assume no specific drug costs for palliative care.

Table 4.9. Drug Costs

Drug	WAC per Unit	Discount from WAC	Net Price per Unit	Annual WAC	Annual Net Price
Upadacitinib (Rinvoq) – 15 mg Tab	$163.89	26%*	$120.56	$59,860	$44,035
Baricitinib (Olumiant) – 2 mg Tab	$71.23	19%	$57.59	$26,017	$21,033
Tofacitinib (Xeljanz) – 5 mg Tab	$74.68	34%	$49.50	$54,552	$36,159
Adalimumab (Humira) – 40 mg/0.8 ml Sol	$2,587.05	34%	$1,696.21	$67,263	$44,102
Methotrexate Sodium (Generic) – 2.5 mg Tab	$2.55	--	$2.55	$796	$796

mg: milligram, ml: milliliter, WAC: wholesale acquisition cost
*Discount calculated as the average discount estimated for the other two JAK inhibitors.

Administration and Monitoring Costs

Oral treatments were assumed to have no administration costs. Subcutaneous treatments include the costs for an annual office visit for training on self-administration, which in our analysis is specific only to adalimumab. However, because patients are attributed a physician's office visit every quarter for disease activity assessment, we assumed one of these visits each year to include training for self-administration and we hence do not separately cost out a physician's office visit for training self-administration for subcutaneous injections. All administration costs inputs are presented below in Table 4.10. All administration costs represent current 2019 US dollar values.

Table 4.10. Administration Costs

	Cost	Source
Subcutaneous Injection Administration (HCPCS Code: 96401)	$80.73	Physician's Fee Schedule, CMS[79]
Office Visit (HCPCS Code: 99213)	$75.32	

CMS: Centers for Medicare & Medicaid Services, HCPCS: Healthcare Common Procedure Coding System

Drug monitoring costs include costs of quarterly tests including comprehensive metabolic test panel, complete blood cell count, lipid panel, acute hepatitis panel, and an additional annual tuberculosis test. Additionally, we also included a cost attributed to a physician's office visit every quarter. Table 4.11 details monitoring cost inputs.

Table 4.11. Monitoring Costs

	Cost*	Source
Tuberculosis Test (HCPCS Code: 86480)	$84.83	CMS[80]
Comprehensive Metabolic Test Panel (HCPCS Code: 80053)	$11.15	
Complete Blood Cell Count (HCPCS Code: 85025)	$10.65	
Lipid Panel (HCPCS Code: 80061)	$14.61	
Acute Hepatitis Panel (HCPCS Code: 80074)	$65.15	

CMS: Centers for Medicare & Medicaid Services, HCPCS: Healthcare Common Procedure Coding System
*Average Medicare Standardized Payment.

Non-Drug Health Care Utilization Costs

The cost of hospitalization was based on the relationship between HAQ and hospitalization, an approach followed by previously published models.[62,65] As seen in Table 4.12, the number of hospitalization days increases with worsening (increasing) HAQ score. The cost of serious infection was assumed to be the weighted average cost of treating pneumonia and cellulitis, two commonly occurring serious infections in RA patients (Table 4.12). This approach is based on that used in the 2017 ICER RA Review.

Table 4.12. Non-Drug Health Care Utilization Costs

HAQ Range	Hospitalization Days per Year	Cost per Day of Hospitalization	Source
HAQ: 0 to <0.5	0.260	$2,470	Carlson et al., 2015[62] Kaiser Family Foundation, 2018[81] IVI RA model[65]
HAQ: 0.5 to <1	0.130		
HAQ: 1 to <1.5	0.510		
HAQ: 1.5 to <2	0.720		
HAQ: 2 to <2.5	1.860		
HAQ: ≥2.5	4.160		
Cost of Serious Infection*	$9,013		Medicare Provider Utilization and Payment Data, 2016[82]

CI: confidence interval, HAQ: Health Assessment Questionnaire
*Weighted average of costs for pneumonia (2/3) and cellulitis (1/3).

Productivity Costs

Societal costs in our model are generated from additional costs from unemployment due to RA. We apply a HAQ-dependent unemployment rate to the baseline unemployment rate (3.8%) and calculate the costs of unemployment, estimated at $225 per day using an hourly wage of $28.11 for an eight-hour workday.[83] A 0.25 increase in HAQ is associated with a 30% increased likelihood of unemployed status.[84]

Sensitivity Analyses

We ran one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses were also performed by jointly varying all model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we performed a threshold analysis by systematically altering the price of interventions to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds between $50,000 and $150,000 per QALY.

Scenario Analyses

In addition to the base-case analysis, we conducted the following scenario analyses:

1) Modified societal perspective that included productivity loss costs as a result of unemployment due to RA
2) Using shorter time horizons of one and five years.

Model Validation

We used several approaches to validate the model. First, preliminary methods were presented to manufacturers, and we subsequently shared draft methods and results with clinical expert reviewers and a health economics expert reviewer. Based on feedback from these individuals and groups, we refined data inputs used in the model. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. During the period that the draft report is under review, we will share a working version of the model to several manufacturers who have shown interest in reviewing the model as an additional validation step. Finally, we compared results to other cost-effectiveness models in this therapy area.

4.3 Results

All analyses except for those using a one-year and a five-year time horizon employ a lifetime time horizon.

Base-Case Results

The total cost and outcomes results for the base case are reported in Tables 4.13 with incremental cost-effectiveness results in Table 4.14. In the comparison of upadacitinib and adalimumab, upadacitinib resulted in only a slight difference in LYs and QALYs compared to adalimumab and had

higher lifetime costs. Upadacitinib use also resulted in higher evLYG compared to adalimumab. The use of upadacitinib resulted in patients spending approximately 0.37 more years (over the course of a lifetime) in remission compared to the use of adalimumab.

Table 4.13. Results for the Base Case for Upadacitinib versus Adalimumab

Treatment	Drug Cost* (Line One)	Total Cost	LYs	QALYs	evLYG	Years in Line One Remission
Upadacitinib + cDMARD	$72,100	$124,000	16.96	11.77	11.78	0.98
Adalimumab + cDMARD	$48,500	$97,300	16.95	11.72	11.72	0.61

cDMARD: conventional disease-modifying antirheumatic drug, evLYG: equal value of life years gained, LY: life year, QALY: quality-adjusted life year

*Only costs of TIM. Does not include cDMARD cost.

The incremental cost-effectiveness ratio for upadacitinib versus adalimumab exceeds the threshold of $150,000 per QALY, and estimates of the cost per LY gained are over $2 million. Cost per evLYG with upadacitinib showed slightly more favorable incremental cost-effectiveness ratios compared to its cost per QALY results, due to the life extension attributed to upadacitinib use versus adalimumab use. The cost per year in remission while on upadacitinib compared to adalimumab is approximately $71,000.

Table 4.14. Incremental Cost-Effectiveness Ratios for Upadacitinib versus Adalimumab

Treatment	Cost per LY Gained	Cost per QALY Gained	Cost per evLYG	Cost per Year in Line One Remission
Upadacitinib + cDMARD vs. Adalimumab + cDMARD	$2.3 million	$482,000	$408,000	$70,500

evLYG: equal value life years gained, LY: life year, QALY: quality-adjusted life year

As stated earlier, we were unable to compare the cost effectiveness of tofacitinib versus adalimumab due to a lack of data. However, we compared the outcomes of the two TIMs relative to their respective conventional DMARD comparators.

Table 4.15. Results for the Base Case for Adalimumab versus Conventional DMARD

Treatment	Drug Cost (Line One)	Total Cost	LYs	QALYs	Years in Line One Remission
Adalimumab + cDMARD	$48,500*	$97,300	16.95	11.72	0.61
cDMARD	$3,300	$46,600	16.94	11.65	0.20

cDMARD: conventional disease-modifying antirheumatic drug, evLYG: equal value of life years gained, LY: life year, QALY: quality-adjusted life year

*Only costs of TIM, does not include cDMARD cost.

Table 4.16. Results for the Base Case for Tofacitinib versus Conventional DMARD

Treatment	Drug Cost (Line One)	Total Cost	LYs	QALYs	Years in Line One Remission
Tofacitinib + cDMARD	$39,100*	$87,900	16.95	11.71	0.49
cDMARD	$2,200	$45,600	16.93	11.64	0.16

cDMARD: conventional disease-modifying antirheumatic drug, evLYG: equal value of life years gained, LY: life year, QALY: quality-adjusted life year

*Only costs of TIM, does not include cDMARD cost.

Results from Tables 4.15 and 4.16 demonstrate that the use of adalimumab or tofacitinib compared to conventional DMARDs results in marginally more LYs and QALYs at almost double the cost.

Sensitivity Analysis Results

Results from the one-way sensitivity analyses are shown on the following pages. For upadacitinib, baseline HAQ, utility estimates, and probability of achieving remission were the top drivers of the QALY (Figure 4.3). Hospitalization rate, the cost of hospitalization, and the probability of achieving remission when treated with upadacitinib were the top divers of total costs (Figure 4.4). Please refer to Appendix E for further results.

Figure 4.3. Tornado Diagram for One-Way Sensitivity Analyses of Upadacitinib versus Adalimumab for QALY Outcomes

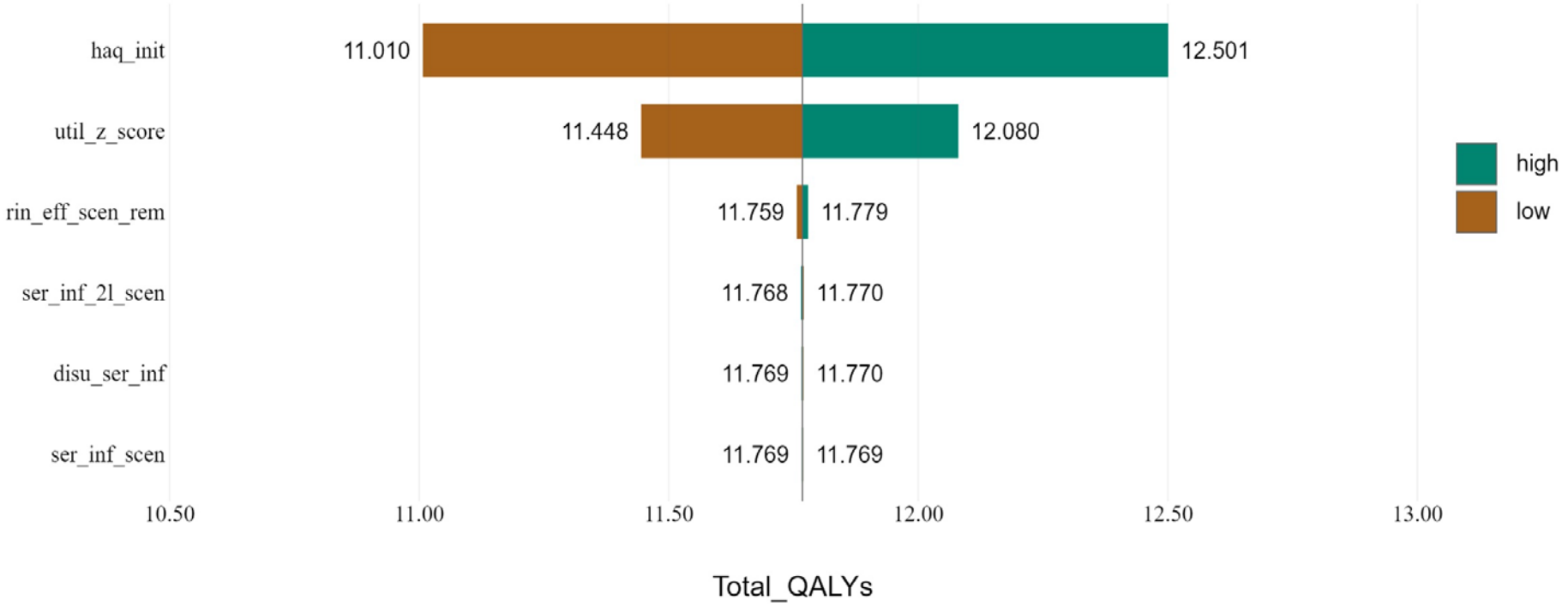
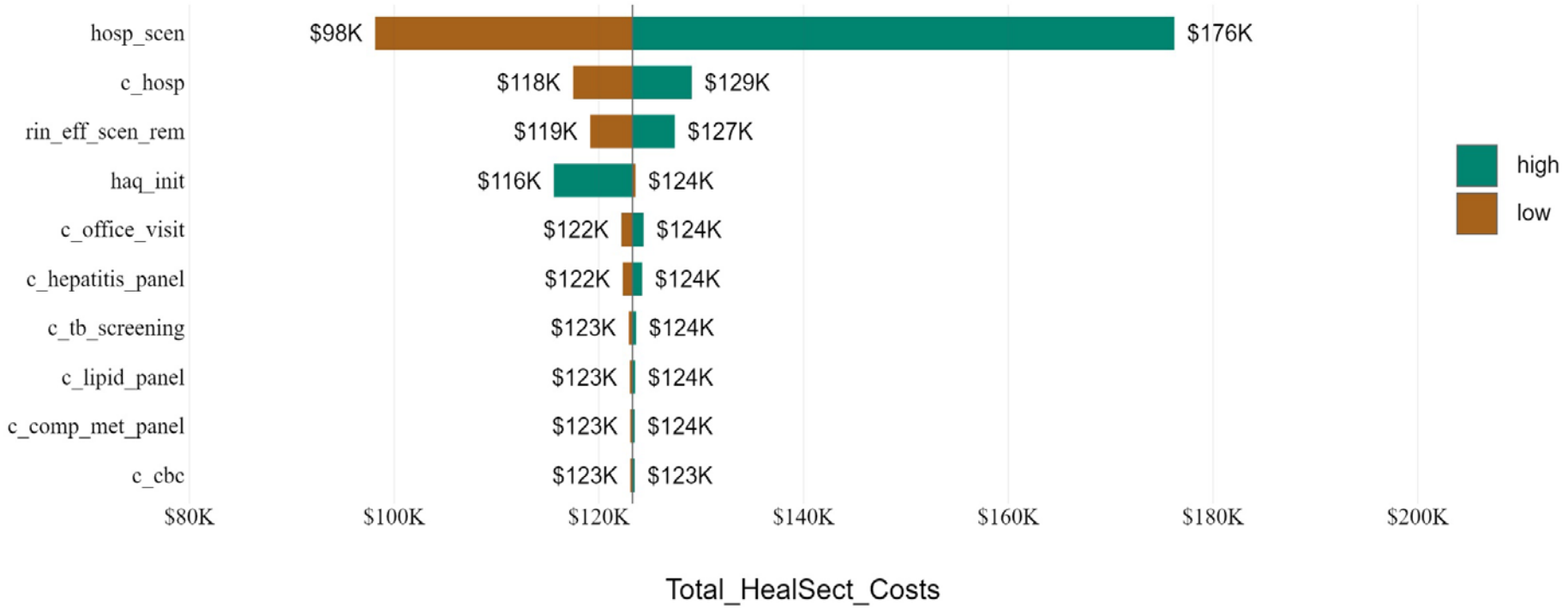


Figure 4.4. Tornado Diagram for One-Way Sensitivity Analyses of Upadacitinib versus Adalimumab for Total Cost Outcomes



A probabilistic sensitivity analysis was also conducted to assess variation in several parameters with over 1,000 Monte Carlo simulations. As shown in Table 4.17 none of the iterations resulted in cost-utility ratios at or under the $150,000 per QALY threshold. A scatter plot showing the distribution of cost-utility ratios over the 1,000 simulations is presented in Appendix E.

Table 4.17. Probabilistic Sensitivity Analysis Results: Upadacitinib versus Adalimumab

	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Upadacitinib + cDMARD	0%	0%	0%

QALY: quality-adjusted life year, cDMARD: conventional disease modifying antirheumatic drug

Scenario Analyses Results

Modified Societal Perspective

Results from the modified societal perspective only impacted total costs in the model. The additional costs of unemployment did not have a substantial impact on the total costs relative to those seen using a health care sector perspective. Similarly, these societal costs did not have a substantial impact on the cost-effectiveness ratios (Table 4.18).

Table 4.18. Cost-Effectiveness Results for Upadacitinib versus Adalimumab from a Modified Societal Perspective

Treatment	Drug Cost* (Line One)	Total Cost	LYs	QALYs	Cost per QALY Gained	Cost per LY Gained
Upadacitinib + cDMARD	$72,100	$124,000	16.96	11.77	$482,000	$2.3 million
Adalimumab + cDMARD	$48,500	$97,900	16.95	11.72	--	--

cDMARD: conventional disease-modifying antirheumatic drug, evLYG: equal value of life years gained, LY: life year, QALY: quality-adjusted life year

*Only costs of TIM, does not include cDMARD cost.

Shorter Time Horizons

We modeled the cost effectiveness of upadacitinib versus adalimumab with shorter time horizons of one and five years. Results from these analyses produced health and economic outcomes that were comparatively smaller in magnitude relative to the base-case analysis, which employed a lifetime time horizon. The small differences in outcomes at these shorter time horizons were smaller than the magnitude of cost differences at these shorter time horizons, leading to more unfavorable incremental cost-effectiveness ratios (Tables 4.19 and 4.20).

Table 4.19. Cost-Effectiveness Results Using a One-Year Time Horizon

Treatment	Total Cost	LYs	QALYs	Incremental Cost per LY Gained*	Incremental Cost per QALY Gained
Upadacitinib + cDMARD	$26,400	0.99	0.675	--	$925,000
Adalimumab + cDMARD	$20,100	0.99	0.668		

cDMARD: conventional disease-modifying antirheumatic drug, LY: life year, QALY: quality-adjusted life year
*No difference up to three decimal places in LYs between the two TIMs.

Table 4.20. Cost-Effectiveness Results Using a Five-Year Time Horizon

Treatment	Total Cost	LYs	QALYs	Incremental Cost per LY Gained*	Incremental Cost per QALY Gained
Upadacitinib + cDMARD	$77.400	4.57	3.16	--	$566,000
Adalimumab + cDMARD	$56,300	4.56	3.12		

cDMARD: conventional disease-modifying antirheumatic drug, LY: life year, QALY: quality-adjusted life year
*No difference up to two decimal places in LYs between the two TIMs.

Threshold Analysis Results

Table 4.21 presents results of our threshold analysis for the price of upadacitinib when compared to adalimumab. The threshold prices required for upadacitinib are reported as annual prices that would achieve selected cost-effectiveness thresholds.

Table 4.21. Threshold Analysis Results for Upadacitinib versus Adalimumab

	Annual WAC	Annual Net Price	Annual Price to Achieve Threshold of:		
			$50,000 per QALY	$100,000 per QALY	$150,000 per QALY
Upadacitinib 15 mg Daily	$59,860	$44,035	$29,800	$31,400	$33,100

QALY: quality-adjusted life year, WAC: wholesale acquisition cost
*Net price calculated based on average discount from WAC, with discount based on the average discount seen with other JAK inhibitors.

Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report and supplemental Appendix materials. We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Additionally, we compared our model results to findings from other published models. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. In our literature review we found several

published economic models that evaluated various treatments for RA. Four models were particularly relevant for our review: 1) the model developed for the 2017 ICER RA Review; 2) a patient-level RA simulation model developed by IVI[65]; 3) a United Kingdom (UK)-specific model developed by Stevenson et al. in 2016 (funded by the National Institute of Care and Excellence in Health [NICE][63]); and 4) a later UK-specific model by Stevenson et al. in 2017, which closely mirrored the methods of the 2016 NICE model.[64]

Overall, the most noticeable differences between our current model and the models mentioned above pertain to: 1) treatment sequence, i.e., in order to isolate the true health and economic benefits of the TIMs included, patients in our model transition to palliative care after failure of first line TIM (other models include a treatment sequence comprising active care with TIMs or conventional DMARDs following failure of first line TIM treatment); and 2) the inclusion of upadacitinib as an intervention of interest in our current model. To our knowledge, our model is the first publicly available economic evaluation of upadacitinib, the most recently approved TIM for the treatment of moderately-to-severely active RA. Thus, all comparisons will focus solely on methods and not necessarily the incremental cost-effectiveness ratios for TIMs as generated by the different models.

While our current model borrows basic structural and parametric model-building approaches from the model developed for the 2017 ICER RA Review, it is also differs in the following important ways:

1) Based on feedback from several stakeholders (including clinical experts) our current model measures levels of disease activity using the DAS28-CRP, an absolute measure of disease activity, instead of the ACR, a relative measure of disease activity that was used in 2017. In 2017 and now, we received mixed feedback on the use of the ACR to measure levels of disease activity. Clinicians noted that the ACR is not as useful in real-world practice for treatment switching decisions. However, most clinical trials employ the ACR as the primary measure of clinical benefit of TIMs. Additionally, despite the fact that the ACR is not the preferred measure of disease activity, we heard that it is used for regulatory approval in several markets. Furthermore, another notable difference is the categories of disease activity used. In 2017, we used four different levels of disease activity as measured by the ACR, but we now use three measures of disease activity. In addition, the subsequent HAQ mapping algorithm used with each disease activity measure is different.
2) In 2017, following failure of line one TIMs in the base case, patients were able to cycle through two additional market baskets of TIMs before transitioning to palliative care. However, in the conventional DMARD comparator arm, patients transitioned directly to palliative care after conventional DMARD failure, which led to a greater magnitude of difference in costs and clinical outcomes between interventions and comparator. In the current model, patients transition directly to palliative care following treatment failure with line one TIMs. Although this approach does not reflect real-world clinical practice,

it was employed to highlight the clinical and economic value of the assessed line one TIMs.

3) The patient population for the cost-effectiveness model in the current review is limited to patients with severely active RA, which is reflective of the trial populations. In 2017, we classify the population more broadly to include patients with moderately-to-severely active disease.
4) In addition to costs, QALYs, and LYs, outcomes in the current model include duration of remission with line one treatment in an attempt to highlight the most preferred clinical benefit expected with the treatments of interest. In 2017, this clinical benefit was assessed more broadly to include responders as defined by the ACR (ACR>20).
5) In our current analysis, we model long-term treatment discontinuation using real-world evidence, though this evidence is generated from data largely representing TNF inhibitors. This, however, follows more recent as well as some earlier approaches for modeling treatment discontinuation.[63,65]
6) In our current model, we use adalimumab, a TNF inhibitor, as the primary comparator, to attempt to answer a more policy-relevant question.

Our current model shares several approaches with the more recently published RA model by IVI.[65] The IVI RA model is a patient-level microsimulation model that allows for customization of individual patient characteristics, choice of disease activity measure to assess treatment response, and other customizable inputs. Our current model differs in being cohort-based, but some key similarities include the use of the same underlying discontinuation rate, the rate of adverse events (serious infection), the use of a similar mapping algorithm to HAQ change and subsequently health-related quality of life, the use of the same long-term HAQ change for TIMs and conventional DMARDs, and use of the same HAQ-dependent hospitalization rate.

A NICE-funded model by Stevenson et al. analyzed the cost effectiveness of several TIMs versus conventional DMARDs in three populations. One population was naïve to conventional DMARD use and two populations included those with conventional DMARD treatment failure and those eligible for TIM use. In the latter populations, all but one TIM treatment strategy included the use of three lines of TIMs followed by conventional DMARDs, and then palliative care. In one TIM strategy assessing tocilizumab as first line treatment, only one additional line of treatment with a TIM was assessed followed by conventional DMARDs and then palliative care. This was done to standardize treatment sequencing in the second-line TIM therapy. This model assessed disease activity and subsequently treatment switching based on an NMA of EULAR response criteria. Similar to our model, the EULAR response was tied to the initial HAQ change, but at six months. The HAQ then governed utility estimates, mortality, and hospitalization in the UK model. Adhering to NICE guidelines, the UK model used a 3.5% discount rate with population characteristics reflective of a UK population with RA. Treatment costs in the model were specific to the UK, and long-term HAQ trajectory was modeled using a latent class growth model approach for the conventional DMARD

arm. Treatment duration was considered the same across TIMs and for conventional DMARDs as long as patients remained on these treatments for at least six months. Discontinuation rates only differed by EULAR response criteria. Only serious infection contributed to adverse events, an approach followed by other models including ours. Unlike in our model, different HRs were used for mortality and were dependent on HAQ ranges, while our model uses a single HR for mortality that is dependent on current HAQ score. Cost-effectiveness results in a population similar to the one we modeled showed cost-utility ratios that exceeded the upper bound of commonly cited threshold ranges (£30,000 per QALY) in the UK for all assessed TIMs.

Another model by Stevenson et al.[64] compares seven TIMs versus conventional DMARDs in two populations: one with moderate-to-severely active RA and the other with severely active RA. Patients were sampled from the British Society for Rheumatology Biologics Register dataset. The methods adopted in this model closely resemble the model developed by the assessment group for the NICE-funded model, as explained above. Base-case results in this model also showed results similar to the 2016 NICE model—cost-utility of each TIM versus conventional DMARD exceeded the commonly cited thresholds of £20,000 to £30,000 per QALY adopted in the UK.

4.4 Summary and Comment

Our aim was to evaluate the cost effectiveness of the three JAK inhibitors versus a TNF inhibitor, adalimumab, in relevant populations. However, gaps in the literature limited our analysis to only comparing upadacitinib to adalimumab in the TIM-naïve population with prior failure of a conventional DMARD. Our base-case findings suggest that upadacitinib provides marginal clinical benefit in comparison to adalimumab, at higher costs. Together, these outcomes translate into cost-effectiveness estimates that exceed commonly cited cost-utility thresholds. Results from the indirect modeling comparison of tofacitinib to adalimumab suggest that for the marginal benefit tofacitinib offers, prices for this drug much higher than the price of adalimumab may not be justified.

The base-case analyses were generally robust to sensitivity analyses. In one-way sensitivity analyses, parameters such as the baseline HAQ, utilities derived from HAQ, probability of remission with upadacitinib, hospitalization rate, and cost of hospitalization influenced the outcomes the most. In probabilistic analyses, approximately none of the simulations were at or fell below the $150,000 per QALY threshold.

Results from our scenario analyses evaluating cost outcomes and incremental cost effectiveness from a modified societal perspective are similar to those seen in the base-case health care sector perspective analysis. Analyses using shorter time horizons result in more unfavorable cost-effectiveness ratios due to smaller differences in outcomes relative to those in the base-case analysis. All analyses suggest upadacitinib at its current assumed net price exceeds commonly cited cost-utility thresholds.

Limitations

Our model has several limitations. First and foremost, our choice of second and subsequent lines of therapy does not reflect real-world practice. Treatment sequencing in RA is non-standardized and dependent on several factors such as individual patient characteristics, treatment efficacy and persistence, physician preference for choice of therapy, and access restrictions. Additionally, there are currently no published standardized guidelines on treatment sequencing. Including different treatment sequences for different initial TIM treatments does not isolate the value of the initial treatments assessed in this analysis. Similarly, assuming a market basket of TIMs as second and subsequent line tends to overestimate the efficacy of initial TIM therapies over the lifetime of the model, which is why we chose to model second and subsequent lines as palliative care.

Second, our model is unable to draw a direct comparison of the value between the new JAK inhibitor, upadacitinib, and the existing JAK inhibitors, tofacitinib and baricitinib, in the TIM-naïve and TIM-experienced populations due to a lack of published data. This is more a limitation of the data than the model and does not inform what clinicians or policymakers would like to know: the most cost-effective choice among the three JAK inhibitors. Similarly, we could only partially answer a policy-relevant question on the choice between JAK inhibitors or adalimumab following conventional DMARD failure or in TIM-experienced patients with severe RA. This again was due to a lack of comparable data among the included treatments.

A third limitation is the use of a standardized treatment discontinuation rate for TIMs and conventional DMARDs. While this may vary in the real world across TIMs and conventional DMARDs, we did not have robust long-term published data for all assessed treatment strategies. Our approach has been used in prior published RA models.[65,85] Fourth, our model does not include TIM adherence over and above treatment discontinuation due to reasons such as patient adverse events, physician preferences, and access restrictions because of a lack of consistent data.

Fifth, in the absence of a validated mapping algorithm from DAS28 to HAQ, we assumed that disease activity as measured using the DAS28 could be mapped to EULAR response categories. Furthermore, as indicated by clinical experts and in published literature, the relationship between DAS28 scores and EULAR responses may not be direct in all cases. For instance, patients may still have residual non-inflammatory joint pain despite a "Good" EULAR response.[86] This indirectly affects the utility mapping functions in this model. Besides algorithms that map such disease activity measures to HAQ and patient health-related utility measures using trial-specific data, longer-term data are required to more accurately map the long-term HAQ trajectories and subsequent utilities that account for multiples lines of treatment.

Finally, the population of focus in our model is patients with severe RA, with treatment efficacy estimates limited to this group. However, in the real world a majority of patients have low disease

activity with fewer having moderate or high disease activity.[87] The value of the interventions assessed may be different in a trial population with less severe RA.

Conclusions

In summary, our analyses indicate that more comparable data is required on the short and long-term efficacy of the JAK inhibitors. Upadacitinib, for which we have trial-specific data, provided marginal clinical benefit over adalimumab but at higher costs, resulting in its incremental cost-utility ratio exceeding commonly cited thresholds.

5. Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. We also recognize that there may be broader contextual issues related to the severity of the condition, whether other treatments are available, and ethical, legal, or other societal priorities that influence the relative value of illnesses and interventions. These general elements are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the comparison of JAK inhibitors to conventional DMARDS or adalimumab. We sought input from stakeholders, including individual patients, patient advocacy organizations, clinicians, and manufacturers, to inform the contents of this section.

Each ICER review culminates in a public meeting of an independent voting Panel of clinicians, patients, and health services researchers. As part of their deliberations, Panel members will judge whether a treatment may substantially impact the considerations listed in Table 5.1. The presence of substantial other benefits or contextual considerations may shift a council member's vote on an intervention's long-term value for money to a different category than would be indicated by the clinical evidence and cost-effectiveness analyses alone. For example, a council member may initially consider a therapy with an incremental cost-effectiveness ratio of $150,000 per QALY to represent low long-term value for money. However, the Panel member may vote for a higher value category if they consider the treatment to bring substantial other benefits or contextual considerations. Conversely, disadvantages associated with a treatment may lead a Council member to vote for a lower value category. A Panel member may also determine that there are no other benefits or contextual considerations substantial enough to shift their vote. All factors that are considered in the voting process are outlined in ICER's value assessment framework. The content of these deliberations is described in the last chapter of ICER's Final Evidence Report, which is released after the public meeting.

This section, as well as the Panel's deliberation, provides stakeholders with information to inform their decisions on a range of issues, including shared decision-making between patients and clinicians, coverage policy development, and pricing negotiations.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to conventional DMARDs or adalimumab, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to conventional DMARDs or adalimumab, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

All three JAK inhibitors are oral drugs, which may be preferred by patients over the parenteral delivery of the other TIMs.

Biologic and conventional DMARDs in general have improved the natural history of RA, with fewer patients developing disabling joint deformities. It is not clear that the JAK inhibitors offer any advantages over the other TIMs.

5.2 Contextual Considerations

RA is a condition with a large impact on the length and quality of life, which has been greatly improved with the introduction of biologic and conventional DMARDs.

6. Value-Based Price Benchmarks

Value-based price benchmarks will be included in the revised Evidence Report that will be released on/about November 7, 2019.

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the total potential budget impact of upadacitinib in adults in the US diagnosed with moderately-to-severely active RA. However, it is important to note that all cost inputs for the budget impact model are generated from our cost-effectiveness model that comprised a population with severely active RA. We used the WAC, an estimate of discounted WAC, and the three threshold prices for upadacitinib (at $50,000, $100,000, and $150,000 per QALY) in our estimates of budget impact.

7.2 Methods

Potential budget impact was defined as the total differential cost of using upadacitinib rather than adalimumab for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon, given the potential for cost offsets to accrue over time and to allow for a more realistic impact on the number of patients treated with the new therapy.

Aligning with its currently approved prescription label, we estimated upadacitinib's eligible population as those adult patients diagnosed with moderately-to-severely active RA in whom prior therapy with methotrexate (conventional DMARD) has failed. While we believe it may also be used in a TIM-experienced population, due to a lack of comparable data against other TIMs, we did not model this in our cost-effectiveness analysis, and subsequently did not include this population in our potential budget impact analysis. Additionally, we do not include a prevalent population of TIM users because we believe it is unlikely that such patients will not switch to using upadacitinib unless they experience inadequate response with or intolerance to their existing TIM. Thus, our estimates of the eligible population represent only a proportion of the larger eligible population that can be treated with upadacitinib.

The estimated the annual incidence of RA in the US is 0.041%, based on an observational study that used electronic medical records data to estimate RA incidence.[88] To this incident population, we then applied estimates of the proportions with moderately-to-severely active RA (36.1%) and those with RA on biologic therapy (52%). These estimates were obtained from an observational cohort study that assessed disease severity based on CDAI measures in RA patients on the CORRONA registry.[89] These estimates were applied to the 2019-23 five-year annual average adult population in the US to arrive at an eligible population size of approximately 20,000 incident patients per year.

ICER's methods for estimating potential budget impact are described in detail elsewhere[90] and have been recently updated. The intent of our revised approach to budget impact is to document the percentage of patients who could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. For 2019-20, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to be approximately $819 million per year for new drugs.

7.3 Results

Table 7.1 illustrates the five-year annualized per-patient potential budget impact of upadacitinib in place of adalimumab in patients in whom conventional DMARDs such as methotrexate have failed, and who are eligible for treatment with a TIM. These results are based on upadacitinib's WAC ($59,900 per year), anticipated net price ($44,000 per year), and the prices to reach thresholds of $150,000, $100,000, and $50,000 per QALY ($33,100, $31,400, and $29,800 per year, respectively) compared to adalimumab.

Table 7.1. Per-Patient Potential Budget Impact Calculations Over a Five-Year Time Horizon

	Average Annual per Patient Budget Impact				
	WAC	Assumed Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Upadacitinib + cDMARD (Annualized Cost)	$26,700	$20,800	$16,700	$16,100	$15,400
Adalimumab + cDMARD (Annualized Cost)	$15,300				
Upadacitinib + cDMARD Potential Budget Impact	$11,400	$5,500	$1,400	$800	$100

cDMARD: conventional disease-modifying antirheumatic drug, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

The average potential budget impact when using upadacitinib's WAC was an additional per-patient cost of approximately $11,400, and approximately $5,500 using its assumed net price. Average potential budget impact at the three cost-effectiveness threshold prices for the drug ranged from approximately $1,400 per patient using the annual price to achieve $150,000 per QALY to approximately $100 using the annual price to achieve a $50,000 per QALY cost-effectiveness threshold.

For upadacitinib, the annual potential budget impact of treating the entire eligible population across all prices (WAC, assumed net price, and the three cost-effectiveness threshold prices for $50,000, $100,000, and $150,000 per QALY) did not exceed the $819 million threshold. The annual potential budget impacts of treating the entire eligible population using the different price levels are compared to the $819 million annual budget impact threshold in Table 7.2. Overall, the

greatest potential annual budget impact we estimated was 77% of the $819 million threshold, using the WAC.

Table 7.2. Estimated Total Population Annual Potential Budget Impact at Different Prices of Upadacitinib for the Eligible Population of 20,000 per Year

Price	Five-Year Annualized Total Population Budget Impact	Percent of Budget Impact Threshold
WAC	$630.5 million	77%
Assumed Net Price	$308.2 million	38%
$150,000 per QALY Threshold Price	$84.8 million	10%
$100,000 per QALY Threshold Price	$51.1 million	6%
$50,000 per QALY Threshold Price	$17.4 million	2%

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

***

This is the second ICER review of treatments for RA.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured Summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and Registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility Criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information Sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study Selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data Collection Process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data Items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of Bias in Individual Studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary Measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of Results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.

Risk of Bias across Studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional Analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study Selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study Characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of Bias within Studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of Individual Studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of Results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of Bias across Studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional Analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of Evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search Strategies for Rheumatoid Arthritis

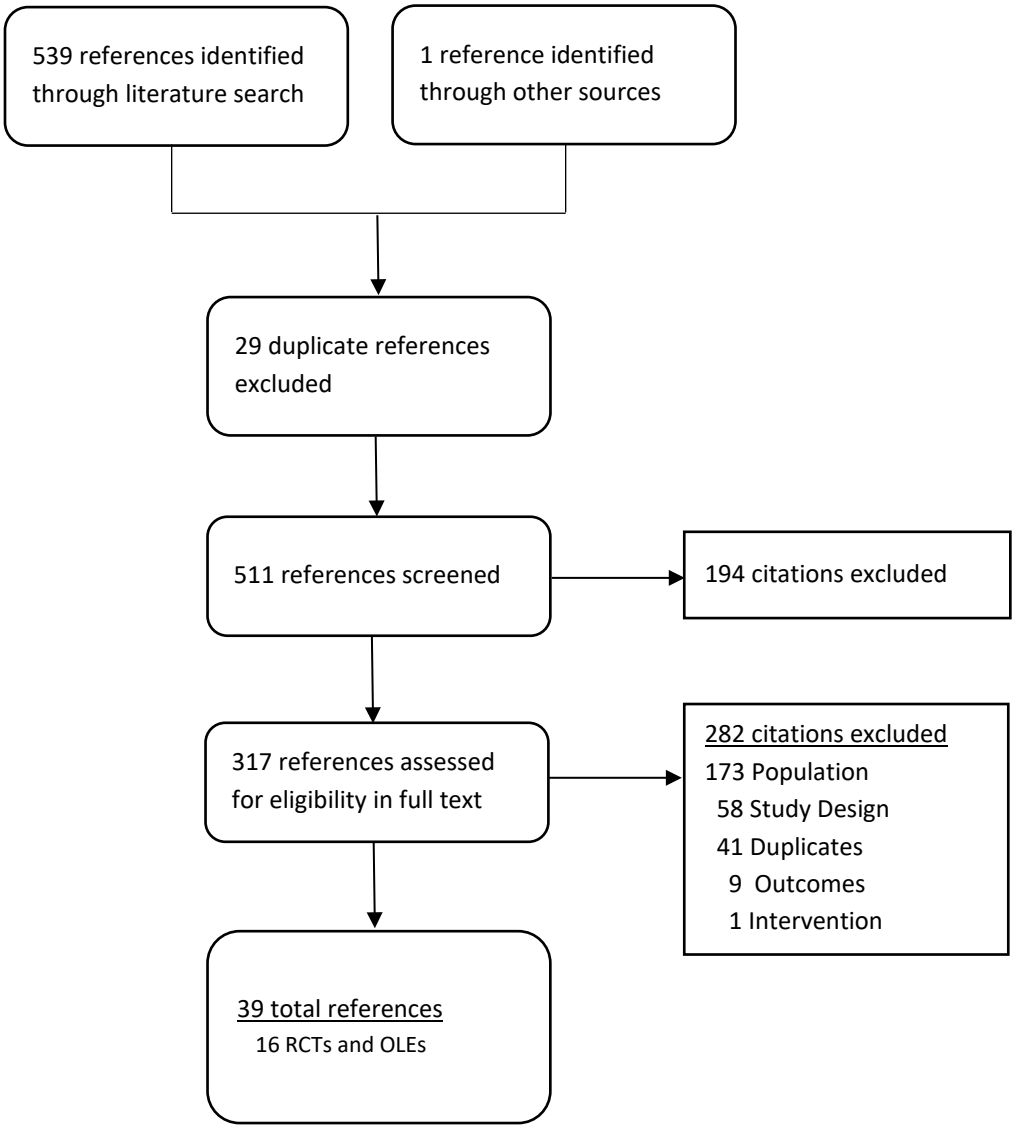
Table A2. Search Strategy of Medline 1996 to Present with Daily Update and Cochrane Central Register of Controlled Trials

No.	Search Terms
#1	((rheumatoid or rheumatic or rheumat$) adj3 (arthrit$ or diseas$ or condition$)).ti,ab.
#2	(tofacitinib or tasocitinib or tofacitinib citrate or Xeljanz).ti,ab
#3	(baricitinib or LY3009104 or INCB028050).ti,ab
#4	(upadacitinib or ABT-494).ti,ab.
#5	(infliximab-dyyb or infliximab dyyb or inflectra or CT-P13 or CT P13).ti,ab
#6	2 or 3 or 4 or 5
#7	1 and 6
#8	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase I or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or videoaudio media).pt
#9	7 not 8
#10	(animals not (humans and animals)).sh.
#11	9 not 10
#12	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt
#13	control Groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
#14	12 or 13
#15	11 and 14
#16	remove duplicates from 15

Table A3. Search Strategy of EMBASE SEARCH

No.	Search Terms
#1	((rheumatoid OR rheumatic OR rheumat*) NEAR/3 (arthrit* OR diseas* OR condition*)):ab,ti
#2	'tofacitinib'/exp OR tofacitinib:ab,ti OR tasocitinib:ab,ti OR 'tofacitinib citrate':ab,ti OR xeljanz:ab,ti
#3	'baricitinib'/exp OR baricitinib:ab,ti
#4	(‘upadacitinib’ OR ‘ABT-494’):ab,ti
#5	‘inflectra’:ab,ti OR ‘infliximab-dyyb’:ab,ti OR ‘CT-P13’:ab,ti
#6	#2 OR #3 OR #4 OR #5
#7	#1 AND #6
#8	#7 AND ('chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#9	#7 NOT #8
#10	#9 AND [english]/lim
#11	#10 AND [medline]/lim
#12	#10 NOT #11

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for JAKs for RA



Appendix B. Previous Systematic Reviews and Technology Assessments

We identified three completed technology assessments of JAK inhibitors for RA, summarized below: two from the National Institute for Health and Care Excellence (NICE), assessing tofacitinib and baricitinib, and one from the Canadian Agency for Drugs and Technologies in Health (CADTH) accessing tofacitinib. We also identified three ongoing technology assessments: one from NICE for upadacitinib and two from CADTH for baricitinib and upadacitinib.

NICE: Tofacitinib for Moderate to Severe RA[91]

The National Institute for Health and Care Excellence (NICE) recommends tofacitinib, with methotrexate, for treating RA, if the disease is severe (a DAS28 score of more than 5.1) and if the patient has responded inadequately to or cannot tolerate DMARDs, including at least one biological DMARD, or they cannot have rituximab. Further, NICE recommends tofacitinib to be used as monotherapy in adults who cannot take methotrexate. Continued use is only recommended if there is a moderate response using the EULAR criteria, six months after starting therapy. Treatment should be withdrawn if EULAR response is not maintained.

NICE: Baricitinib for Moderate to Severe RA[92]

NICE recommends baricitinib, with methotrexate, as an option for treating RA in lieu of DMARDs, if disease is severe (a DAS28 score of more than 5.1), or the patient cannot tolerate rituximab, only if they have responded inadequately to intensive therapy with a combination of conventional DMARDs. Baricitinib can also be used as monotherapy for patients who cannot take methotrexate.

CADTH (2014). Tofacitinib (Xeljanz) Clinical Review Report. CADTH Clinical Review Report.[93]

CADTH conducted a systematic review of tofacitinib for the treatment of RA. Five RCTs met the inclusion criteria and evaluated the efficacy and safety of 5 mg twice daily or 10 mg twice daily tofacitinib, with one study also evaluating adalimumab versus placebo. Studies evaluated patients who had experienced an inadequate response to TNF inhibitors, non-biologic DMARDs, and/or methotrexate. There were also included studies that evaluated tofacitinib as monotherapy and others, with patients on a background treatment of DMARDs. All five trials assessed the same endpoints including: ACR20, HAQ-DI, and DAS28. CADTH recommends tofacitinib, in combination with methotrexate, be considered as an option for the treatment of RA in patients with moderate to severe disease or as monotherapy in those who are intolerant to methotrexate treatment. Tofacitinib was found to have a safety profile similar to that of biologic DMARDs and the economic

analysis concluded that treatment with tofacitinib is more costly than treatment with infliximab, tocilizumab (intravenous), or tocilizumab (subcutaneous).

NICE: Upadacitinib for Treating Moderate to Severe Rheumatoid Arthritis [ID1400]. Expected publication date 18 March 2020

NICE is currently evaluating the clinical and cost effectiveness of upadacitinib for treating moderate to severe RA. Proposed comparators include combination therapy with conventional DMARDs, conventional DMARDS with dose escalation, and best supportive care for patients who have not responded well to therapy with conventional DMARDs. For patients with severe RA who have not responded well to conventional DMARDS only, comparators include biological DMARDs or JAK inhibitors (baricitinib and tofacitinib). For patients with severe RA who have not responded well to either DMARDs or at least one TNF inhibitor, comparators include rituximab with methotrexate and TNF inhibitors.

Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review: Baricitinib

CADTH recommends reimbursement for baricitinib as monotherapy or in combination with methotrexate (with or without additional conventional DMARDs) for the treatment of adult patients with moderately to severely active RA who have responded inadequately to one or more DMARDs. CADTH requires that patients discontinue therapy if a treatment response (i.e., achievement of ACR20) is not achieved by 12 weeks. Patients should be receiving care from a rheumatologist and their daily dose of baricitinib should be limited to 2 mg. CADTH has placed a pricing condition on baricitinib that stipulates that the drug plan cost of treatment with baricitinib should result in cost-savings compared with the drug plan cost of treatment with the least costly alternative biologic DMARD.

Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review: Upadacitinib [SR0614-000], Expected publication date December 2019

CADTH is currently evaluating the clinical and cost effectiveness of upadacitinib for the treatment of moderate to severe RA.

Appendix C. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Baricitinib (BAR)					
A Study of Baricitinib (LY3009104) in Participants With Rheumatoid Arthritis (RA-BRIDGE) NCT03915964 Eli Lilly and Company	Phase IV, Randomized, parallel assignment, open label Enrolled: 2,600	Intervention: • BAR low dose • BAR high dose Comparator: • TNFi	Inclusions: • Documented evidence of VTE prior to study • At least age 60 • Body mass index (BMI) ≥30 • Age 50 to less than 60 years old • BMI 25 to less than 30 Exclusions: • Previous TNFi use • Pregnant or breastfeeding • Multiple VTE • Cancer • Herpes zoster, serious infection, active tuberculosis • A live vaccine within 4 weeks of start • Participated in a clinical trial within 4 weeks of start • History of IV drug use, or any other illicit drug use	Time from first dose of study treatment to first event of venous thromboembolism	February 1, 2026
An Extension Study in Participants with Moderate to Severe Rheumatoid Arthritis (RA-BEYOND) NCT01885078 Eli Lilly and Company	Phase III, multicenter, randomized, parallel assignment, quadruple masking Enrolled: 2,944	Intervention: • BAR 2 mg • BAR 4 mg Comparator: Placebo	Inclusions: • Have completed the final active treatment in study JADV Exclusions: • Have significant uncontrolled cerebro-cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, neuropsychiatric disorders, or abnormal laboratory values • Have a known hypersensitivity to baricitinib or any component of this investigational product	Number of participants with one or more drug related adverse events (AEs) or serious adverse events (SAEs)	March 22, 2024

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
			• Had investigational product permanently discontinued at any time during a previous baricitinib study • Had temporary investigational product interruption at the final study visit		
Examination of Efficacy and Safety of Baricitinib in RA Patients NCT03755466 Shinshu University	Phase II, non-randomized, paralleled assignment Enrolled: 90	Intervention: BAR Comparator: • TOF • bDMARDs	Inclusions: • RA patients Exclusions: • RA patients who are allergic to the interventions • Refused study guidelines • Pregnant	1) Assessment of disease activity in RA patients for 1 year treated by BAR, bDMARDs, or TOF 2) The efficacy and adverse events of each drug for 1 year in the RA patients	November 20, 2023
Tofacitinib					
Efficacy and Safety of GSK3196165 Versus Placebo and Tofacitinib in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Methotrexate NCT03980483 GlaxoSmithKline	52-week, Phase III, randomized, double-blind Enrolled: 1,500	Interventions: • GSK319165 • TOF 5 mg • Comparator: Placebo to TOF • cDMARD	Inclusions: • ≥18 years of age • Has had RA for ≥6 months and was not diagnosed before 16 years of age Has active disease, as defined by having both: • ≥6/68 tender/painful joints, and • ≥6/66 swollen joints • Has at least 1 bone erosion present on hand/wrist or foot radiographs • Has had an inadequate response to cDMARD, despite currently taking cDMARD 15-25 mg/week oral or injected Exclusions:	Proportion of participants achieving ACR20 at Week 12: superiority comparison with placebo	July 3, 2021

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
			• Has had any active and/or recurrent infections (excluding recurrent fungal infections of the nail bed) or has required management of acute or chronic infections. • Has received prior treatment with an antagonist of GM-CSF or its receptor or targeted cDMARDs • Has received prior treatment with a bDMARD that was discontinued due to an inadequate response		
Efficacy and Safety of GSK3196165 Versus Placebo and Tofacitinib in Participants With Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Conventional Synthetic (cs)/Biologic (b) Disease Modifying Anti-rheumatic Drugs (DMARDs) NCT03970837 GlaxoSmithKline	52-week, Phase III, randomized, double-blind Enrolled: 1,500	Intervention: • GSK319165 • TOF 5 mg Comparator: • Placebo to GSK31916 • Placebo to TOF • cDMARDs	Inclusions: • ≥18 years of age • Has had RA for ≥6 months and was not diagnosed before 16 years of age • Have active disease Exclusions: • History of other inflammatory rheumatologic or systemic autoimmune disorder, other than Sjogren's syndrome secondary to RA, that may confound the evaluation of the effect of the study intervention • Has had any active and/or recurrent infections or has required management of acute or chronic infections • Has received prior treatment with an antagonist of GM-CSF or its receptor or targeted cDMARDs	Proportion of participants achieving ACR20 at Week 12: superiority comparison with placebo	July 2, 2021
Upadacitinib (UPA)					
A Study To Investigate The Safety and Efficacy of ABBV-105 Alone or in	Phase II, randomized, parallel assignment,	Intervention: • UPA • ABBV-105	Inclusion • Diagnosis of RA for ≥3 months based on 2010 ACR/EULAR classification criteria • ≥ 6 swollen joints and ≥6 tender joints	Change from baseline in DAS28 and CRP at 12 weeks	January 15, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Combination With Upadacitinib (ABBV-599 Combination) in Participants With Active Rheumatoid Arthritis NCT03682705 AbbVie	quadruple masking Enrolled: 240	Comparator: Placebo	• hsCRP ≥3mg/L • treated for ≥3 months with ≥1 bDMARD therapy but continue to exhibit active RA • Receiving cDMARD therapy ≥3 months and on stable dose for ≥4 weeks prior to the first dose of study drug • Participants must have discontinued all bDMARDs prior to first dose of study drug Exclusion: • Participants had prior exposure to JAK inhibitor for greater than two weeks including but not limited to UPA, TOF, BAR, and filgotinib • A washout period of ≥30 days is required for any JAK inhibitor prior to the first dose of study drug		
A Study with Upadacitinib (ABT-494) in Subjects from Chine and Selected Countries with Moderately to Severely Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (cDMARDs)	Phase III, randomized, parallel assignment, quadruple masking Enrolled: 450	Intervention: UPA Comparator: Placebo	Inclusions: • Diagnosis of rheumatoid arthritis for ≥3 months who also fulfilled the 2010 ACR/EULAR classification criteria for RA • Participants had been receiving cDMARD therapy ≥3 months and on a stable dose for ≥4 weeks prior to first dose of study drug • Participants with prior exposure to at most a bDMARD may be enrolled (up to 20%) • Participants must have discontinued bDMARD therapy prior to the first dose of study drug Participant meet both of the following disease criteria: 1. ≥6 swollen joints and ≥76 tender joints at screening and baseline visits and	Proportion of participants achieving ACR 20 response	September 10, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
NCT02955212 AbbVie			2. High-sensitivity c-reactive protein ≥ upper limit of normal at screening visit Exclusions: • Prior exposure to any JAK inhibitor • Participants who are considered inadequate responders to bDMARD therapy • History of arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA		
A Phase 3 Study to Compare Upadacitinib to Abatacept in Subjects with Rheumatoid Arthritis on Stable Dose of Conventional Synthetic Disease-Modifying Antirheumatic Drugs (cDMARDs) Who Have an Inadequate Response of Intolerance to Biologic DMARDs (SELECT-CHOICE) NCT03086343 AbbVie	Phase III, randomized, active-controlled, quadruple masking Enrolled: 614	Intervention: UPA Active Comparator: Abatacept Comparator: Placebo	Inclusions: • Diagnosis of RA • Participants have been treated for ≥3 months with ≥1 bDMARD therapy but continue to exhibit RA or had to discontinue due to intolerability or toxicity • Participants have been receiving cDMARD therapy ≥3 months and on a stable dose for ≥4 weeks prior to first dose of study drug Exclusions: • Prior exposure to JAK inhibitors • Prior exposure to abatacept • History of arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA	Change in DAS28 CRP (non-inferiority)	February 29, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Phase 2b/3, Randomized, Double-Blind Study Comparing ABT-494 to Placebo in Japanese Subjects With Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (cDMARDs) and Have an Inadequate Response to cDMARDs (SELECT-SUNRISE) NCT02720523 AbbVie	Phase II, randomized, quadruple masking Enrolled: 197	Intervention: ABT-494 (UPA) Comparator: Placebo	Inclusions: • Diagnosis of RA for ≥3 months who also fulfill the 2010 ACR/EULAR classification criteria for RA • Subjects have been receiving cDMARD therapy ≥3 months and on a stable dose for ≥4 weeks prior to the first dose of study drug • Subject has ≥6/66 swollen joints and ≥6/68 tender joints at screening and baseline visits • Subjects with prior exposure to at most bDMARD may be enrolled (up to 20% of total number of subjects) after the required washout period. Exclusions: • Prior exposure to any JAK-inhibitor • Subjects who are considered inadequate responders (lack of efficacy) to bDMARD therapy, after minimum 3 months treatment, as determined by the Investigator • History of any arthritis with onset prior to age 17 years or current diagnosis of inflammatory joint disease other than RA	Proportion of subjects achieving ACR 20 response at Week 12	July 19, 2020
Infliximab-dyyb					
National Observational Study On The Use Of Inflectra An Infliximab Biosimilar In Real Life (ReFLECT) NCT02925338 Pfizer	Observational, cohort, prospective Enrolled: 1,200	QOL questionnaire	Inclusions: • Adult patients treated with Inflectra regardless of treatment phase in Crohn's disease, ulcerative colitis, RA, ankylosing spondylitis, or psoriatic arthritis • Pediatric patients treated with Inflectra regardless of treatment phase time Exclusions:		September 23, 2020

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
			• Patients who refused to access their medical file for collection of their medical data • Patients treated with Inflectra for psoriasis • Patients with past history of hypersensitivity to infliximab • Patients with tuberculosis or any other severe infection such as sepsis, abscess, or opportunistic infection • Patients with moderate to severe heart failure		

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

ACR: American College of Rheumatology, bDMARD: biologic disease-modifying antirheumatic drug, cDMARD: conventional disease-modifying antirheumatic drug, CRP: C-reactive protein, DAS: Disease Activity Score 28, EULAR: European League Against Rheumatology, IV: intravenous, JAK: Janus kinase, TNFi: tumor necrosis factor inhibitor, VTE: venous thromboembolism

Appendix D. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to baricitinib, tofacitinib, upadacitinib, and infliximab-dyyb. These included the prescribing information, manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the USPSTF to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[94] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

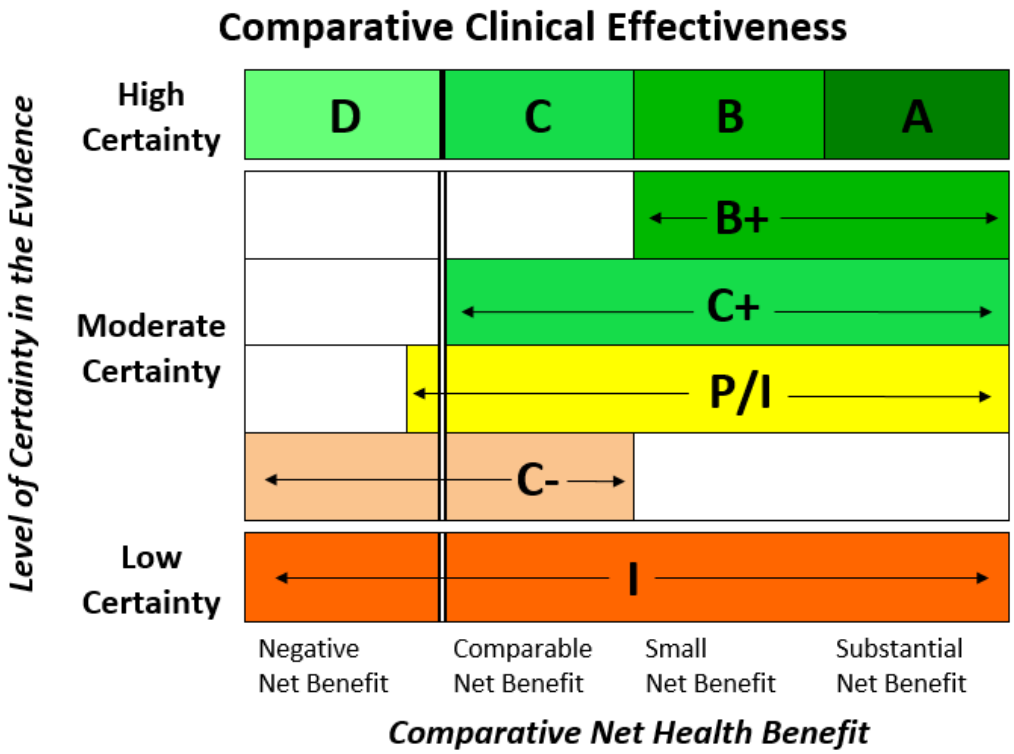
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating

We used the ICER Evidence Rating Matrix (see Figure D1) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[27]

Figure D1. ICER Evidence Rating Matrix



A = "Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" *- High certainty of a small net health benefit*
C = "Comparable" *- High certainty of a comparable net health benefit*
D = "Negative" *- High certainty of an inferior net health benefit*
B+ = "Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C- = "Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I = "Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table D1. Included Studies

Trial Name (Author & Year of Publication)	Study Sponsor	Study Design and Duration of Follow-Up	Geographic Location of Study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Primary Outcomes
Baricitinib (BAR)						
RA-BUILD[95] **Dougados 2017**	Eli Lilly & Co.	RCT, Phase III, 12-week follow-up	182 centers in 22 countries	1) BAR 2 mg + cDMARD 2) cDMARD	Concomitant use of cDMARDs, non-steroidal and anti-inflammatory drugs and/or corticosteroids were permitted	ACR20 response at 12 weeks
RA-BEACON[50] **Genovese 2016**	Eli Lilly & Co.	RCT, Phase III, 24-week follow-up	178 centers in 24 countries	1) BAR 2 mg + cDMARD 2) cDMARD	Patients who had received other bDMARDs could participate if bDMARDs were discontinued at least 4 weeks before randomization	ACR20 response at 12 weeks
RA-BEYOND[96,97] **(abstract)** **Genovese 2017** **Van Der Heijde 2019**	Eli Lilly & Co.	Phase III, multicenter, open-label extension, duration up to 7 years	Multicenter	1) continued BAR 4 mg 2) Stepped down to BAR 2 mg	Patients were eligible for RA-BEYOND if they had completed one of the originating studies (RA-BUILD, RA-BEGIN, RA-BEAM). Patients were not eligible if they were hypersensitive to BAR or permanently discontinued during the originating study	Disease activity at 12 weeks
Keystone 2015[98]	Eli Lilly & Co.	RCT, Phase IIb, 24-week follow-up	69 centers in 9 countries	1) BAR 2 mg + cDMARD 2) cDMARD	Moderately to severely active RA patients were excluded if they had previously used bDMARDs	ACR20 response at 12 weeks
Tofacitinib (TOF)						
ORAL Sync[41,99] **Kremer 2013** **Strand 2017**	Pfizer	RCT, Phase III, double-blind, 1-year trial duration	114 centers in 19 countries	1) TOF 5 mg 2) Placebo (advanced to TOF after 6 months)	Inclusions: active RA diagnosis, an ESR ≥22mm/h or a CRP ≥66.7 nmol/L Exclusions: previous treatment with lymphocyte-depleting therapies within 1 year of randomization or alkylating agents at any time	• ACR20 response at 24 weeks • DAS28-4(ESR) defined remission ≤2.6 • Change in HAQ-DI score • Safety assessments
ORAL Step[49,100] **Burmester 2013** **Strand 2015**	Pfizer	Phase III, double-blind, parallel	82 centers in 19 countries	1) TOF 5 mg 2) Placebo (advanced to TOF after 3 months)	Inclusions: ≥18 years with diagnosis of active moderate-to-severe RA with previous inadequate response or	• ACR20 response rate • Mean change from baseline HAQ-DI

Trial Name (Author & Year of Publication)	Study Sponsor	Study Design and Duration of Follow-Up	Geographic Location of Study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Primary Outcomes
		group study, 24-week follow-up			intolerance to one or more approved TNFi Exclusions: hemoglobin ≤90.0 g/L	• Rates of DAS28-4(ESR) ≤ 2.6 (all at 12 weeks)
ORAL Scan[44] Van der Heijde 2013	Pfizer	RCT, Phase III, double blind, parallel-group, placebo-controlled,12-month interim analysis, 24-month follow up	111 centers in 5 continents	1) TOF 5 mg + cDMARD 2) Placebo (advanced to TOF + cDMARD after 6 months)	Inclusions: ≥18 years with active RA diagnosis Exclusions: hemoglobin <9.0 gm/dl and hematocrit < 30%, white blood cell count <3.0 x 10^9/liter, absolute neutrophil count <1.2 x 10^9/liter, or platelet count <100 x 109/liter	• ACR20 response rate at 24 weeks • Mean change from base in SHS score at 24 weeks • Mean change from baseline in HAQ-DI score at 12 weeks • Rates of remission (DAS28-ESR ≤2.6) at 24 weeks
ORAL Strategy[43,101] Fleischmann 2017 Strand 2017	Pfizer	RCT, Phase IIIb/4, head-to-head, non-inferiority, 1-year duration	194 centers in 25 countries	1) TOF 5 mg 2) TOF 5 mg + cDMARD 3) ADA 40 mg + cDMARD	Inclusions: ≥18 years with active RA despite methotrexate therapy Exclusions: patient had previous treatment with TNFi, contraindications for study treatment, history of infections requiring treatment within 2 weeks	ACR50 response rate at 24 weeks
ORAL Standard[42,102] Van Vollenhoven 2013 Strand 2016	Pfizer	RCT, Phase III, 12-month follow-up,	multicenter	1) TOF 5 mg + cDMARD 2) ADA 40 mg 3) Placebo followed by TOF 5 mg + cDMARD	Active RA and inadequate response to cDMARD. Excluded if treated with adalimumab previously	• ACR 20 response at 24 weeks • Disease activity at 12 weeks • Proportions achieving DAS28-CRP ≤2.6 at 24 weeks

Trial Name (Author & Year of Publication)	Study Sponsor	Study Design and Duration of Follow-Up	Geographic Location of Study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Primary Outcomes
Nakamura 2018[103]	No financial support for research and/or authorship	Prospective, randomized study, 1-year follow-up	Japan	1) TOF 5 mg 2) non-TNF biologics	Moderately to severely active RA and inadequate response to bDMARD or methotrexate	• Disease status at 12 months • Percent change of DAS28-CRP from baseline to 12 months
Charles-Schoeman 2016[38]	Pfizer	Pooled analysis of Phase II and III studies	N/A	bDMARD Naïve 1) TOF 5 mg 2) cDMARD bDMARD-IR 3) TOF 5 mg 4) cDMARD	Phase II studies Patients had to be IR to a bDMARD or cDMARD Phase III studies Patients had an IR to a bDMARD or cDMARD	• ACR20, 50 or 70 response • DAS28 -ESR, CDAI, and SDAI at 3 and 6 months
Kremer 2012[104]	Pfizer	RCT, Phase IIb, double-blind, 24-weeks follow-up	multicenter	1) TOF 5 mg + cDMARD 2) cDMARD	Moderately to severely active RA and receiving methotrexate. Excluded if they had any hematopoietic disorders or comorbidities	• ACR20 response at 12 weeks • Proportion achieving DAS28-CRP <2.6 at 12 weeks
Upadacitinib (UPA)						
SELECT-MONOTHERAPY[105,106] **Smolen 2019 Strand 2018**	AbbVie	RCT, double-blind, cDMARD arm crossed over to UPA 15mg or 30mg at 14 weeks; patients followed up to 5 years	24 countries	1) UPA 15 mg 2) UPA 30 mg 3) cDMARD	Moderate to severe active RA and inadequate response to methotrexate	• ACR20 response at 14 weeks • Proportion achieving DAS28-CRP ≤3.2 (NRI)
SELECT-COMPARE[39] **Fleischman 2019**	AbbVie	RCT, double-blind, 48 weeks follow-up. At weeks 14,	286 sites in 41 countries	1) UPA 15 mg + cDMARD 2) ADA 40 mg +	Moderate to severe active RA and inadequate response to methotrexate	• ACR20 response at 12 weeks

Trial Name (Author & Year of Publication)	Study Sponsor	Study Design and Duration of Follow-Up	Geographic Location of Study	Interventions (n) & Dosing Schedule	Inclusion and Exclusion Criteria	Primary Outcomes
		18, and 22, patients without an improvement of ≥20% in TJC and SJC received rescue therapy, switching from PBO to UPA, UPA to ADA, or ADA to UPA		cDMARD 3) Placebo + cDMARD		• Proportion achieving DAS28-CRP <2.6 at 12 weeks
SELECT-BEYOND[48,106] **Genovese 2018** **Strand 2018**	AbbVie	RCT, double-blind, 24 weeks randomized treatment, followed by a double-blinded extension of up to 5 years	26 countries	1) UPA 15 mg + cDMARD 2) UPA 30 mg + cDMARD 3) Placebo + cDMARD	Moderate to severe active RA and inadequate response to bDMARDs	• ACR20 response at 12 weeks • Proportion achieving DAS28-CRP ≤3.2 at 12 weeks
SELECT-NEXT[40,106] **Burmester 2018** **Strand 2018**	AbbVie	RCT, Phase III, 12-week study followed by an ongoing double-blind extension of up to 5 years	35 countries	1) UPA 15 mg + cDMARD 2) UPA 30 mg + cDMARD 3) Placebo + cDMARD	Moderate to severely active RA with inadequate response to cDMARDs	• ACR20 response at 12 weeks • Proportion achieving DAS28-CRP ≤3.2 (NRI) at 12 weeks

ACR: American College of Rheumatology, ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, CDAI: clinical disease activity index, cDMARD: conventional disease-modifying antirheumatic drug, CRP: C-reactive protein, DAS: Disease Activity Score 28, ESR: erythrocyte sedimentation rate, EULAR: European League Against Rheumatology, HAQ-DI: Health Assessment Questionnaire without Disability Index, IR: inadequate response, IV: intravenous, JAK: Janus kinase, NRI: non-responder imputation, RA: rheumatoid arthritis, SDAI: simple disease activity index, SHS: Sharp score as modified by van der Heijde, SJC: swollen joint count, TJC: tender joint count, TNFi: tumor necrosis factor inhibitor

Table D2. Quality of Studies

Study	Adequate Randomization	Allocation Concealment	Patient Blinding	Staff Blinding	Outcome Adjudication Blinding	Completeness of Follow Up	Intention to Treat Analysis	Incomplete Data Addressed	Selective Outcome Reporting	Industry Funding	Freedom from Bias	Overall Quality
Baricitinib												
RA-BUILD[95] Dougados 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
RA-Beacon[50] Genovese 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
RA-BEYOND[96,97] Genovese 2017 Van der Heijde 2019	N/A – pooled open label extension study	N/A	No	No	No	No	No	Yes	No	Yes	No	Poor
Keystone 2015[98]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Tofacitinib												
ORAL Sync[41] Kremer 2013 Strand 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
ORAL Step[49] Burmester 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
ORAL Scan[44] Van der Heijde 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
ORAL Strategy[43] Fleischmann 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
ORAL Standard[42] Van Vollenhoven 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Nakamura 2018[103]	Yes	Unclear	Unclear	Unclear	Unclear	No	Yes	No	No	No	Unclear	Poor
Charles-Schoeman 2016[38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Kremer 2012[104]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good

Study	Adequate Randomization	Allocation Concealment	Patient Blinding	Staff Blinding	Outcome Adjudication Blinding	Completeness of Follow Up	Intention to Treat Analysis	Incomplete Data Addressed	Selective Outcome Reporting	Industry Funding	Freedom from Bias	Overall Quality
Upadacitinib												
SELECT-MONOTHERAPY[105] Smolen 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
SELECT-COMPARE[39] Fleischmann 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
SELECT-BEYOND[48] Genovese 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
SELECT-NEXT[40] Burmester 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

N/A: not available

Table D3. Baseline Characteristics I

Study	Intervention	N	Female, n (%)	Age, Mean Years (SD)	Disease Duration, Mean Years (SD)	Previous DMARD use, n (%)		
						1	2	≥3
Baricitinib (BAR)								
RA-BUILD[95] Dougados 2017RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	184 (80.0)	52 (12)	8 (8)	104 (45.0)	61 (27.0)	61 (27.0)
	cDMARD	228	189 (83.0)	51 (13)	7 (8)	96 (42.0)	81 (36.0)	50 (22.0)
RA-BEACON[50] Genovese 2016RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	137 (79.0)	55 (11)	14 (8)	69 (40.0)‡	55 (32.0)‡	50 (29.0)‡
	cDMARD	176	145 (82.0)	56 (11)	14 (10)	81 (46.0)‡	47 (27.0)‡	47 (27.0)‡
RA-BEYOND[96,97] Genovese 2017 (Abstract), Van Der Heijde 2019	Continued BAR 4 mg	147	N/A					
	Stepped down to BAR 2 mg	146	N/A					
Keystone 2015[98]	BAR 2 mg	52	43 (85.0)	51 (13)	5.5 (4.4)	0 (0)‡	0 (0)‡	0 (0)‡
	cDMARD	98	86 (87.0)	49 (12)	5.4 (4.3)	0 (0)‡	0 (0)‡	0 (0)‡
Tofacitinib (TOF)								
ORAL Sync[41] Kremer 2013ORAL Sync[41] Kremer 2013	TOF 5 mg	315	264 (83.8)	52.7 (11.7)	8.1 (Range: 0.2-39.9)	NR	NR	NR
	Placebo (advanced to TOF 5 mg at 6 months)	79	63 (79.7)	50.8 (11.2)	9.5 (Range: 0.3-39.3)	NR	NR	NR
ORAL Step[49] Burmester 2013ORAL Step[49] Burmester 2013	TOF 5 mg	133	113 (85.0)	55.4 (11.5)	13.0 (Range: 1.2-55.0)	84 (63.2)†	37 (27.8)†	11 (8.3)†
	Placebo	132	106 (80.3)	54.4 (11.3)	11.3 (Range: 0.4-47.0)	86 (65.2)†	37 (28.0)†	9 (6.8)†
ORAL Scan[44] Van der Heijde 2013ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	269 (83.8)	53.7 (11.6)	8.9 (Range: 0.3–43.0)	NR	NR	NR
	Placebo (advanced to TOF 5 mg at 6 months)	81	65 (80.2)	53.2 (11.5)	8.8 (Range: 0.6–30.8)	NR	NR	NR
ORAL Strategy[43] Fleischmann 2017ORAL Strategy[43] Fleischmann 2017	TOF 5 mg	384	319 (83.0)	49.7 (12.2)	Median (Range): 6.1 (0.2-41.6)	NR	NR	NR
	TOF 5 mg + cDMARD	376	311 (83.0)	50.0 (13.4)	Median (Range): 5.4 (0.0-43.5)	NR	NR	NR
	ADA + cDMARD	386	320 (83.0)	50.7 (13.4)	Median (Range): 6.0 (0.3-42.8)	NR	NR	NR
ORAL Standard[42] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	174 (85.3)	53 (11.9)	7.6 (NR)	NR	NR	NR
	ADA 40 mg + cDMARD	204	162 (79.4)	52.5 (11.7)	8.1 (NR)	NR	NR	NR
	Placebo (followed by TOF 5 mg + cDMARD)	56	43 (76.8)	55.5 (13.7)	6.9 (NR)	NR	NR	NR

Study	Intervention	N	Female, n (%)	Age, Mean Years (SD)	Disease Duration, Mean Years (SD)	Previous DMARD use, n (%)		
						1	2	≥3
Nakamura 2018[103]	TOF 5 mg	22	13 (59.1)	67.2 (1.7)	3.4 (0.7)	NR	NR	NR
	Non-TNF biologics	20	17 (85.0)	68.3 (1.2)	3.5 (1.0)	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1071	911 (85.0)	52.6 (11.9)	7.7 (7.4)	0 (0)†	0 (0)†	0 (0)†
	bDMARD Naïve: cDMARD	651	539 (82.8)	52.0 (12.5)	8.2 (8.2)	0 (0)†	0 (0)†	0 (0)†
	bDMARD-IR: TOF 5 mg	259	218 (84.2)	54.7 (11.1)	12.1 (9.1)	120 (60.9)†	≥2: 77 (39.1)†	
	bDMARD-IR: cDMARD	193	158 (81.9)	54.0 (11.6)	11.2 (8.6)	97 (62.6)†	≥2: 58 (37.4)†	
Kremer 2012[104]	TOF 5 mg + cDMARD	71	57 (80.3)	52 (12.8)	9.0 (Range: 0.5-46.0)	≥1: 4 (5.6)		
	Placebo + cDMARD	69	56 (81.2)	53 (13.4)	9.2 (Range: 0.5-39.0)	≥1: 2 (2.0)		
Upadacitinib (UPA)								
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	174 (80.2)	54.5 (12.2)	7.5 (8.9)*	NR	NR	NR
	UPA 30 mg	215	170 (79.1)	53.1 (12.7)	6.5 (7.0)*	NR	NR	NR
	MTX	216	179 (82.9)	55.3 (11.1)	5.8 (6.6)*	NR	NR	NR
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	521 (80.0)	54 (12)	8 (8)*	NR	NR	NR
	ADA 40 mg + cDMARD	327	259 (79.2)	54 (12)	8 (8)*	NR	NR	NR
	Placebo + cDMARD	651	512 (78.6)	54 (12)	8 (8)*	NR	NR	NR
SELECT-BEYOND[48] Genovese 2018SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	137 (83.5)	56.3 (11.3)	12.4 (9.4)*	86 (52.4)‡	40 (24.4)‡	38 (23.2)‡
	UPA 30 mg + cDMARD	165	138 (84.1)	57.3 (11.6)	12.7 (9.7)*	66 (40.0)‡	51 (30.9)‡	47 (28.5)‡
	Placebo + cDMARD	169	143 (84.6)	57.6 (11.4)	14.5 (9.2)*	83 (49.1)‡	46 (27.2)‡	40 (23.7)‡
SELECT-NEXT[40] Burmester 2018SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	182 (82.4)	55.3 (11.5)	7.3 (7.9)*	27 (12.2%) previous bDMARD exposure		
	UPA 30 mg + cDMARD	219	172 (78.5)	55.8 (11.3)	7.3 (7.9)*	28 (12.8%) previous bDMARD exposure		
	Placebo + cDMARD	221	166 (75.1)	56.0 (12.2)	7.2 (7.5)*	29 (13.1%) previous bDMARD exposure		

ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, cDMARD: conventional disease-modifying antirheumatic drug, N: total number, n: number, N/A: not available, NR: not reported, SD: standard deviation

*Reported as time since RA diagnosis.

†Previous TNFi.

‡Previous bDMARD.

Table D4. Baseline Characteristics II

Study	Intervention	N	Tender Joint Count-68, Mean (SD)	Swollen Joint Count-66, Mean (SD)	DAS28-ESR, Mean (SD)	DAS28-CRP, Mean (SD)	HAQ-DI, Mean (SD)
Baricitinib (BAR)							
RA-BUILD[95] Dougados 2017RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	24 (14)	14 (9)	6.3 (1.0)	5.6 (1.0)	1.5 (0.62)
	cDMARD	228	24 (15)	13 (7)	6.2 (1.0)	5.5. (0.9)	1.5 (0.60)
RA-BEACON[50] Genovese 2016RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	31 (16)	19 (12)	6.7 (1.0)	6.0 (0.9)	1.7 (0.55)
	cDMARD	176	28 (16)	17 (11)	6.6 (0.9)	5.9 (0.9)	1.8 (0.57)
RA-BEYOND[96,97] Genovese 2017 (Abstract) RA-BEYOND[96,97] Genovese 2017 (Abstract), Van Der Heijde 2019	Continued BAR 4 mg	147	N/A				
	Stepped down to BAR 2 mg	146					
Keystone 2015[98]	BAR 2 mg	52	23.0 (12.6)	17.0 (9.3)	6.2 (0.8)	5.4 (0.9)	1.1 (0.7)
	cDMARD	98	22.2 (12.1)	15.8 (8.6)	6.3 (0.8)	5.5 (0.9)	1.2 (0.7)
Tofacitinib (TOF)							
ORAL Sync[41] Kremer 2013ORAL Sync[41] Kremer 2013	TOF 5 mg	315	25.0 (15.3)	14.5 (10.3)	6.3 (1.0)	NR	1.4 (0.69)
	Placebo (advanced to TOF 5 mg at 6 months)	79	27.2 (16.8)	14.6 (9.7)	6.4 (1.0)	NR	1.5 (0.64)
ORAL Step[49] Burmester 2013	TOF 5 mg	133	28.4 (18.3)	16.2 (10.1)	6.5 (1.1)	5.4 (1.0)	1.6 (0.7)
	Placebo	132	28.2 (16.7)	17.2 (10.7)	6.4 (1.1)	5.4 (1.0)	1.6 (0.7)
ORAL Scan[44] Van der Heijde 2013ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	24.1 (14.0)	14.1 (8.2)	6.3 (NR)	5.2 (NR)	1.4 (0.7)
	Placebo (advanced to TOF 5 mg at 6 months)	81	23.3 (NR)	14.0 (NR)	6.3 (NR)	5.1 (NR)	1.4 (NR)
ORAL Strategy[43] Fleischmann 2017	TOF 5 mg	384	15.4 (6.5)†	11.2 (5.6)†	6.5 (0.9)	5.7 (0.9)	1.6 (0.6)
	TOF 5 mg + cDMARD	376	15.6 (6.5)†	11.8 (5.7)†	6.6 (0.9)	5.8 (0.9)	1.6 (0.6)
	ADA + cDMARD	386	15.2 (6.7)†	11.0 (5.4)†	6.5 (1.0)	5.7 (1.0)	1.6 (0.6)
ORAL Standard[107] Van Vollenhoven 2013ORAL Standard[107] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	28.5 (NR)	16.7 (NR)	6.6 (NR)	5.4 (NR)	1.5 (NR)
	ADA 40 mg + cDMARD	204	26.7 (NR)	16.4 (NR)	6.4 (NR)	5.3 (NR)	1.5 (NR)
	Placebo followed by TOF 5 mg + cDMARD	56	26.6 (NR)	16.9 (NR)	6.6 (NR)	5.6 (NR)	1.5 (NR)
Nakamura 2018[103]	TOF 5 mg	22	NR	NR	NR	4.2 (0.1)	0.7 (0.2)

Study	Intervention	N	Tender Joint Count-68, Mean (SD)	Swollen Joint Count-66, Mean (SD)	DAS28-ESR, Mean (SD)	DAS28-CRP, Mean (SD)	HAQ-DI, Mean (SD)
	Non-TNF biologics	20	NR	NR	NR	4.2 (0.2)	0.7 (0.2)
Charles-Schoeman 2016[38]	bDMARD naïve: TOF 5 mg	1071	25.1 (14.7)	15.1 (9.2)	6.4 (1.0)	NR	1.4 (0.7)
	bDMARD naïve: cDMARD	651	23.8 (13.9)	15.2 (9.0)	6.3 (1.0)	NR	1.3 (0.7)
	bDMARD-IR: TOF 5 mg	259	28.8 (16.7)	16.1 (9.4)	6.5 (1.0)	NR	1.6 (0.6)
	bDMARD-IR: cDMARD	193	27.8 (16.9)	16.8 (10.6)	6.4 (1.1)	NR	1.6 (0.6)
Kremer 2012[104]	TOF 5 mg + cDMARD	71	21.5 (1.5)	14.1 (0.9)	6.1 (NR)	5.1 (NR)	1.4 (0.1)
	Placebo + cDMARD	69	21.6 (1.6)	15.7 (1.1)	6.1 (NR)	5.3 (NR)	1.2 (0.1)
Upadacitinib (UPA)							
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	24.5 (15.1)	16.4 (10.9)	NR	5.6 (0.9)	1.5 (0.7)
	UPA 30 mg	215	24.8 (15.2)	16.9 (10.2)	NR	5.6 (1.1)	1.5 (0.7)
	cDMARD	216	25.2 (16.0)	16.9 (11.5)	NR	5.6 (1.0)	1.5 (0.7)
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	26 (15.0)	17 (10.0)	6.4 (1.0)	5.8 (1.0)	1.6 (0.6)
	ADA 40 mg + cDMARD	327	26 (15.0)	16 (9.0)	6.5 (1.0)	5.9 (1.0)	1.6 (0.6)
	Placebo + cDMARD	651	26 (14.0)	16 (9.0)	6.5 (1.0)	5.8 (0.9)	1.6 (0.6)
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	27.8 (16.3)	17.0 (10.8)	NR	5.9 (1.0)	1.7 (0.6)
	UPA 30 mg + cDMARD	165	27.3 (15.2)	17.2 (11.4)	NR	5.8 (0.9)	1.6 (0.6)
	Placebo + cDMARD	169	28.5 (15.3)	16.3 (9.6)	NR	5.8 (1.0)	1.6 (0.6)
SELECT-NEXT[40] Burmester 2018SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	25.2 (13.8)	16.0 (10.0)	NR	5.7 (1.0)	1.5 (0.6)
	UPA 30 mg + cDMARD	219	26.2(14.3)	16.2 (10.6)	NR	5.7 (0.9)	1.5 (0.6)
	Placebo + cDMARD	221	24.7 (15.0)	15.4 (9.2)	NR	5.6 (0.8)	1.4 (0.6)

ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, cDMARD: conventional disease-modifying antirheumatic drug, CRP: C-reactive protein, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, GA: global assessment, HAQ-DI: Health Assessment Questionnaire without Disability Index, N: total number, n: number, N/A: not available, NR: not reported, SD: standard deviation, VAS: visual analogue scale

*Combined placebo arms (advanced to TOF 5 mg or 10 mg).

†Out of 28.

Table D5. Baseline Characteristics III

Study	Intervention	N	CDAI, Mean (SD)	SDAI, Mean (SD)	Morning Stiffness Duration, Min (SD)	Morning Stiffness Severity, 0-10 Scale	Concomitant cDMARD Use, n (%)		
							Methotrexate	Hydroxy-chloroquine	Sulfa-salazine
Baricitinib (BAR)									
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	NR	38 (13)	NR	NR	NR	NR	NR
	cDMARD	228	NR	37 (12)	NR	NR	NR	NR	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	NR	45 (14)	NR	NR	141 (81.0)	NR	NR
	cDMARD	176	NR	43 (14)	NR	NR	143 (81.0)	NR	NR
RA-BEYOND[96,97] Genovese 2017 (Abstract) RA-BEYOND[96,97] Genovese 2017 (Abstract), Van Der Heijde 2019	Continued BAR 4 mg	147	N/A						
	Stepped down to BAR 2 mg	146	N/A						
Keystone 2015[98]	BAR 2 mg	52	37.7 (12.2)	38.9 (12.2)	73.1 (42.2)	NR	52 (100)	11 (21.0)	7 (13.0)
	cDMARD	98	37.1 (12.3)	38.6 (12.5)	101.7 (110.7)	NR	98 (100)	16 (16.0)	14 (14)
Tofacitinib (TOF)									
ORAL Sync[41] Kremer 2013	TOF 5 mg	315	NR	NR	NR	NR	250 (79.4)	47 (14.9)	39 (12.4)
	Placebo (advanced to TOF 5 mg at 6 months)	79	NR	NR	NR	NR	61 (77.2)	10 (12.7)	12 (15.2)
ORAL Step[49] Burmester 2013	TOF 5 mg	133	NR	NR	NR	NR	133 (100)	0 (0)	0 (0)
	Placebo	132	NR	NR	NR	NR	132 (100)	0 (0)	0 (0)
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	NR	NR	NR	NR	321 (100)	0 (0)	0 (0)
	Placebo (advanced to TOF 5mg at 6 months)	81	NR	NR	NR	NR	81 (100)	0 (0)	0 (0)

Study	Intervention	N	CDAI, Mean (SD)	SDAI, Mean (SD)	Morning Stiffness Duration, Min (SD)	Morning Stiffness Severity, 0-10 Scale	Concomitant cDMARD Use, n (%)		
							Methotrexate	Hydroxy-chloroquine	Sulfa-salazine
ORAL Strategy[43] Fleischmann 2017	TOF 5 mg	384	38.6 (12.6)	40.2 (13.0)	NR	NR	0 (0)	0 (0)	0 (0)
	TOF 5 mg + cDMARD	376	39.7 (12.7)	41.6 (13.2)	NR	NR	376 (100)	0 (0)	0 (0)
	ADA + cDMARD	386	38.2 (12.9)	39.8 (13.3)	NR	NR	386 (100)	0 (0)	0 (0)
ORAL Standard[107] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	NR	NR	NR	NR	204 (100)	0 (0)	0 (0)
	ADA 40 mg + cDMARD	204	NR	NR	NR	NR	204 (100)	0 (0)	0 (0)
	Placebo followed by TOF 5 mg + cDMARD	56	NR	NR	NR	NR	56 (100)	0 (0)	0 (0)
Nakamura 2018[103]	TOF 5 mg	22	19.7 (2.2)	NR	NR	NR	19 (86.4)	NR	NR
	Non-TNF biologics	20	18.7 (2.2)	NR	NR	NR	13 (65.0)	NR	NR
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1071	37.0 (12.3)	38.9 (12.9)	NR	NR	NR	NR	NR
	bDMARD Naïve: cDMARD	651	36.2 (12.8)	38.0 (13.2)	NR	NR	NR	NR	NR
	bDMARD-IR: TOF 5 mg	259	38.6 (12.5)	40.7 (13.4)	NR	NR	NR	NR	NR
	bDMARD-IR: cDMARD	193	38.3 (13.3)	39.9 (13.7)	NR	NR	NR	NR	NR
Kremer 2012[104]	TOF 5 mg + cDMARD	71	NR	NR	NR	NR	71(100)	0 (0)	0 (0)
	cDMARD	69	NR	NR	NR	NR	69 (100)	0 (0)	0 (0)
Upadacitinib (UPA)									
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	38.0 (13.1)	39.4 (13.4)	144.2 (215.1)	NR	0 (0)	0 (0)	0 (0)
	UPA 30 mg	215	38.4 (13.8)	40.0 (14.3)	133.9 (152.7)	NR	0 (0)	0 (0)	0 (0)
	cDMARD	216	37.8 (14.4)	39.2 (14.6)	153.0 (221.7)	NR	216 (100)	0 (0)	0 (0)

Study	Intervention	N	CDAI, Mean (SD)	SDAI, Mean (SD)	Morning Stiffness Duration, Min (SD)	Morning Stiffness Severity, 0-10 Scale	Concomitant cDMARD Use, n (%)		
							Methotrexate	Hydroxy-chloroquine	Sulfa-salazine
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	40 (13)	NR	142 (188)	NR	651 (100)	0 (0)	0 (0)
	ADA 40 mg + cDMARD	327	40 (13)	NR	146 (185)	NR	327 (100)	0 (0)	0 (0)
	Placebo + cDMARD	651	40 (13)	NR	142 (170)	NR	651 (100)	0 (0)	0 (0)
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	41.7 (13.3)	43.3 (13.8)	140.4 (189.7)	6.8 (2.1)	137 (83.5)	7 (4.3)	6 (3.7)
	UPA 30 mg + cDMARD	165	40.1 (12.3)	41.7 (12.8)	184.5 (284.9)	6.5 (2.2)	135 (81.8)	14 (8.5)	9 (5.5)
	Placebo + cDMARD	169	41.0 (13.3)	42.6 (13.9)	138.4(178.6)	6.8 (2.3)	139 (82.2)	11 (6.5)	8 (4.7)
SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	38.3 (11.9)	39.9 (12.5)	152.4 (241.9)	6.1 (2.4)	169 (76.5)	NR	NR
	UPA 30 mg + cDMARD	219	38.6 (12.7)	40.0 (13.1)	128.6 (156.0)	6.2 (2.2)	175 (79.9)	NR	NR
	Placebo + cDMARD	221	37.8 (11.8)	39.0 (11.9)	138.9 (214.0)	6.1 (2.2)	190 (86.0)	NR	NR

ADA: adalimumab, bDMARD: bDMARD: biologic disease-modifying antirheumatic drug, CDAI: clinical disease activity index, cDMARD: conventional disease-modifying antirheumatic drug, IR: inadequate response, n: number, N: total number, NR: not reported, SDAI: simple disease activity index, TNF: tumor necrosis factor

Table D6. Baseline – Patient Reported Outcomes

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)	Physicians' GA, 0-100 mm VAS (SD)	Pain, 0-100 mm VAS (SD)	FACIT-F	SF-36	
							PCS	MCS
Baricitinib (BAR)								
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	62 (20)	64 (17)	60 (21)	NR	NR	NR
	cDMARD	228	60 (21)	62 (17)	57 (23)	NR	NR	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	67 (19)	67 (17)	62 (22)	NR	NR	NR
	cDMARD	176	66 (19)	67 (19)	65 (19)	NR	NR	NR
RA-BEYOND[96,97] Genovese 2017, Van Der Heijde 2019	Continued BAR 4 mg	147	N/A					
	Stepped down to BAR 2 mg	146						
Keystone 2015[98]	BAR 2 mg	52	NR					
	cDMARD	98						
Tofacitinib (TOF)								
ORAL Sync[41,99] Kremer 2013, Strand 2017	TOF 5 mg	315	59.0 (22.9)	NR	57.1 (23.8)	29.0 (11.1)	32.4 (7.8)	40.9 (12.6)
	Placebo	158	57.9 (23.3)	NR	57.1 (22.8)	29.7 (9.0)	32.7 (7.6)	41.7 (11.6)
ORAL Step[49,100] Burmester 2013, Strand 2015	TOF 5 mg	133	64.7 (23.2)	NR	65.7 (22.8)	27.8 (11.1)	30.7 (9.3)	42.8 (12.7)
	Placebo*	132	61.9 (22.9)	NR	60.7 (23.5)	27.0 (11.5)	30.0 (8.0)	41.3 (13.3)
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	316	58.1 (23.6)	59.4 (15.9)	58.4 (23.1)	NR	NR	NR
	Placebo*	156	54.1 (22.9)	55.9 (17.4)	55.0 (23.9)*	NR	NR	NR
ORAL Strategy[43,101] Fleischmann 2017, Strand 2017	TOF 5 mg	384	60.1 (21.4)	59.7 (17.7)	61.2 (21.7)	NR	NR	NR
	TOF 5 mg + cDMARD	376	61.7 (22.0)	60.7 (18.0)	60.7 (22.4)	NR	NR	NR
	ADA + cDMARD	386	60.2 (23.5)	60.3 (19.6)	60.6 (22.6)	NR	NR	NR
ORAL Standard[102,107] Van Vollenhoven 2013, Strand 2016	TOF 5 mg + cDMARD	198	60.0 (21.4)	NR	59.2 (21.1)	28.2 (10.5)	33.1 (7.7)	39.8 (11.7)
	ADA 40 mg + cDMARD	199	57.1 (22.3)	NR	56.3 (22.0)	27.9 (10.1)	32.7 (6.8)	40.6 (11.7)
	Placebo followed by TOF 5 mg + cDMARD	104	54.3 (21.4)	NR	55.0 (21.4)	30.4 (10.3)	33.1 (6.3)	43.3 (10.7)
Nakamura 2018[103]	TOF 5 mg	22	NR					
	Non-TNF biologics	20	NR					
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1071	59.5 (22.9)	60.3 (16.8)	58.6 (23.4)	NR	NR	NR

	bDMARD Naïve: cDMARD	651	56.3 (22.8)	59.1 (17.0)	56.1 (23.2)	NR	NR	NR
	bDMARD-IR: TOF 5 mg	259	64.4 (22.0)	65.1 (17.4)	64.3 (21.9)	NR	NR	NR
	bDMARD-IR: cDMARD	193	61.2 (22.7)	63.4 (16.6)	60.1 (23.5)	NR	NR	NR
Kremer 2012[104]	TOF 5 mg + cDMARD	71	56.5 (2.3)	54.6 (2.8)	54.9 (3.2)	NR	NR	NR
	cDMARD	69	58.3 (1.8)	51.9 (3.2)	51.2 (3.3)	NR	NR	NR
Upadacitinib (UPA)								
SELECT-MONOTHERAPY[105,106] Smolen 2019, Strand 2018	UPA 15 mg	217	62.2 (22.3)	65.7 (18.5)	62.3 (22.5)	NR	33.3 (7.9)	44.1 (11.3)
	UPA 30 mg	215	59.4 (22.8)	62.6 (17.8)	61.9 (22.1)	NR	33.9 (7.8)	44.5 (11.5)
	cDMARD	216	59.6 (21.8)	62.1 (17.5)	62.5 (21.3)	NR	33.3 (7.3)	45.1 (11.0)
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	64 (22.0)	66 (17.0)	66 (21.0)	27 (11)	33 (7)	NR
	ADA 40 mg + cDMARD	327	66 (21.0)	65 (18.0)	66 (21.0)	26 (11)	32 (7)	NR
	Placebo + cDMARD	651	64 (21.0)	66 (18.0)	65 (21.0)	27 (11)	33 (7)	NR
SELECT-BEYOND[48,106] Genovese 2018, Strand 2018	UPA 15 mg + cDMARD	164	67.2 (19.6)	68.7 (16.6)	68.2 (19.8)	NR	30.6 (7.8)	44.0 (11.7)
	UPA 30 mg + cDMARD	165	64.7 (21.1)	66.4 (15.6)	65.3 (20.7)	NR	45.9 (12.3)	45.9 (12.3)
	Placebo + cDMARD	169	66.3 (22.7)	66.9 (16.9)	68.9 (21.0)	NR	31.6 (7.2)	45.9 (12.6)
SELECT-NEXT[40,106] Burmester 2018, Strand 2018	UPA 15 mg + cDMARD	221	63.1 (21.9)	64.3 (16.2)	64.1 (19.5)	28.1 (11.1)	33·4 (7.4)	45.9 (10.9)
	UPA 30 mg + cDMARD	219	62.8 (20.3)	63.0 (18.0)	64.0 (19.8)	27.5 (12.6)	32.6 (7.9)	46.1 (12.0)
	Placebo + cDMARD	221	60.3 (20.5)	64.4 (17.7)	61.5 (20.8)	28.3 (11.5)	33.1 (7.7)	46.5 (11.7)

bDMARD: biologic disease modifying anti-rheumatic drug, cDMARD: conventional disease modifying anti-rheumatic drug, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, GA: Global Assessment, IR: inadequate response, MCS: Mental Component Score, N: total number, N/A: not available, NR: not reported, PCS: Physical Component Score, SF: Short Form, TNF: tumor necrosis factor, VAS: visual analogue scale

*Total placebo arm (advanced to either TOF 5 mg or 10 mg at 6 months).

Table D7. Outcomes at Three Months (12-14 Weeks) – ACR and EULAR Response

Study	Interventions	N	ACR20, n (%)	ACR50, n (%)	ACR70, n (%)	EULAR, n (%)
Baricitinib						
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	151 (66.0)†	77 (34.0)†	41 (18.0)†	NR
	cDMARD	228	90 (39.0)	29 (13.0)	7 (3.0)	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	85 (49.0)†	35 (20.0)‡	23 (13.0)‡	NR
	cDMARD	176	48 (27.0)	14 (8.0)	4 (2.0)	NR
RA-BEYOND[96,97] Genovese 2017 (Abstract), Van Der Heijde 2019	Continued BAR 4 mg	147	NR			
	Stepped down to BAR 2 mg	146				
Keystone 2015[98]	BAR 2 mg + cDMARD	52	28 (54.0)¶¶	9 (17.5) ¶¶	5 (8.5) ¶¶	- Good: 9 (17.0) - Good/moderate: 43 (81.0)†
	cDMARD	98	41 (41.0) ¶¶	11 (11.0) ¶¶	2 (2.5) ¶¶	- Good: 16 (16.0) - Good/moderate: 51 (51.0)
Tofacitinib						
ORAL Sync[41] Kremer 2013	TOF 5 mg + cDMARD	315	177 (56.1)†	86 (27.3)†	27 (8.6)†	NR
	cDMARD	159	43 (27.0)	15 (9.4)	3 (1.9)	NR
ORAL Step[49] Burmester 2013	TOF 5 mg + cDMARD	132	55 (41.7)‡	35 (26.5)*	18 (13.6)*	Remission: 8 (6.1)*
	cDMARD	131	32 (24.4)	11 (8.4)	2 (1.5)	Remission: 0 (0)
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg + cDMARD	321	NR	93 (28.9)†¶¶	38 (11.7)‡¶¶	NR
	Placebo (advanced to TOF 5 mg at 6 months)	81	NR	7 (8.3)¶¶	3 (3.1)¶¶	NR
ORAL Strategy[43] Fleischmann 2017	TOF 5 mg	384	240 (62.5)¶¶	122 (31.7)¶¶	49 (12.7)¶¶	NR
	TOF 5 mg + cDMARD	376	264 (70.2)¶¶	156 (41.4)¶¶	70 (18.5)¶¶	NR
	ADA + cDMARD	386	265 (68.5)¶¶	146 (37.7)¶¶	56 (14.3)¶¶	NR
ORAL Standard[107] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	125 (60.9)¶¶	71 (34.4)¶¶	(11.5)¶¶	NR
	ADA 40 mg + cDMARD	204	115 (56.4)¶¶	49 (23.6)¶¶	(7.8)¶¶	NR
	Placebo followed by TOF 5 mg + cDMARD	56	16 (28.6)¶¶	6 (10.7)¶¶	(1.1)¶¶	NR
Nakamura 2018[103]	TOF group	22	NR	NR	NR	NR
	Non-TNF group	20	NR	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1043	629 (60.3)†	341 (32.7)†	135 (12.9)†	NR
	bDMARD Naïve: cDMARD	638	169 (26.5)	62 (9.7)	18 (2.8)	NR

Study	Interventions	N	ACR20, n (%)	ACR50, n (%)	ACR70, n (%)	EULAR, n (%)
	bDMARD-IR: TOF 5 mg	258	112 (43.4)†	63 (24.4)†	25 (9.7)§	NR
	bDMARD-IR: cDMARD	191	47 (24.6)	20 (10.5)	6 (3.1)	NR
Kremer 2012[104]	TOF 5 mg + cDMARD	71	36 (50.7)§	25 (35.2)§	13 (18.0)§	Good: 21 (29.4)§
	Placebo + cDMARD	69	23 (33.3)	12 (17.4)	4 (5.8)	Good: 11 (15.2)
Upadacitinib						
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	147 (67.7)*	91 (41.9)*	49 (22.6)*	NR
	UPA 30 mg	215	153 (71.2)*	112 (52.1)*§	71 (33.0)*	NR
	cDMARD	216	89 (41.2)	33 (15.3)	6 (2.8)	NR
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	462 (71.0)†¶	293 (45.0)†§§	163 (25.0)†§§	NR
	ADA 40 mg + cDMARD‡	327	206 (63.0)	95 (29.1)	43 (13.1)	NR
	Placebo + cDMARD	651	234 (35.9)	98 (15.1)	33 (5.1)	NR
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	106 (64.6)*	56 (34.3)*	19 (11.7)	NR
	UPA 30 mg + cDMARD	165	93 (56.4)*	59 (34.7)*	39 (23.5)*	NR
	cDMARD	169	48 (28.4)	20 (11.8)	11 (6.7)	NR
SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	141 (63.8)*	84 (38.0)*	46 (20.8)*	NR
	UPA 30 mg + cDMARD	219	145 (66.2)*	94 (42.9)*	59 (26.9)*	NR
	cDMARD	221	79 (35.7)	33 (14.9)	13 (5.9)	NR

ACR: American College of Rheumatology, ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, cDMARD: conventional disease-modifying antirheumatic drug, EULAR: European League Against Rheumatology, n: number, N: total number, NR: not reported

*p<0.0001.

†p<0.001

‡p<0.01.

§p<0.05 vs. placebo.

§§p<0.001.

¶p<0.05 for upadacitinib vs. adalimumab.

¶¶Data was digitized and should be interpreted with caution.

#p-value not reported for adalimumab vs. placebo.

Table D8. Outcomes at Three Months (12-14 Weeks) – DAS28, SDAI, CDAI

Study	Interventions	N	DAS28-CRP, n (%)		DAS28-ESR, n (%)		CDAI, n (%)		SDAI, n (%)	
			≤3.2	≤2.6	≤3.2	≤2.6	≤10	≤2.8	≤11	≤3.3
Baricitinib										
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	83 (36.0)†	60 (26.0)†	48 (21.0)†	25 (11.0)†	78 (34.0)‡	23 (10.0)†	76 (33.0)‡	21 (9.0)†
	cDMARD	228	39 (17.0)	21 (9.0)	16 (7.0)	5 (2.0)	48 (21.0)	5 (2.0)	46 (20.0)	3 (1.0)
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	42 (24.0)†	20 (11.0)§	23 (13.0)‡	11 (6.0)‡	42 (24.0‡	6 (3.0)	39 (22.0)†	4 (2.0)
	cDMARD	176	16 (9.0)	71 (4.0)	8 (4.0)	2(1.0)	20 (11.0)	4 (2.0)	16 (9.0)	4 (2.0)
RA-BEYOND[96,97] Genovese 2017 (Abstract) Van Der Heijde 2019	Continued BAR 4 mg	147	Change from baseline: 0.14 (0.70)		Change from baseline: 0.10 (0.73)		136 (92.5)	57 (38.8)	Change from baseline: 0.69 (3.55)	
	Stepped down to BAR 2 mg	146	Change from baseline: 0.36 (0.77)§		Change from baseline: 0.35 (0.89)§		123 (84.2)§	54 (37.0)	Change from baseline: 2.19 (6.33)§	
Keystone 2015[98]	BAR 2 mg	52	12 (23.0)	8 (15.0)§	8 (15.0)	5 (8.0)§	NR	4 (6.0)	NR	4 (6.0)
	cDMARD	98	19 (19.0)	4 (4.0)	10 (10.0)	1 (1.0)	NR	1 (1.0)	NR	1 (1.0)
Tofacitinib										
ORAL Sync[41] Kremer 2013	TOF 5 mg	284	NR	NR	NR	23 (8.4)†	NR	NR	NR	NR
	Placebo	153	NR	NR	NR	1 (0.5)	NR	NR	NR	NR
ORAL Step[49] Burmester 2013	TOF 5 mg	119	NR	NR	17 (14.3)§	8 (6.7)§	NR	NR	NR	8 (6.7)*
	Placebo	120	NR	NR	6 (5.0)	2 (1.7)	NR	NR	NR	0 (0)
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo advanced to TOF 5 mg (at 6 months)	81	NR	NR	NR	NR	NR	NR	NR	NR
ORAL Strategy[43] Fleischmann 2017	TOF 5 mg	384	NR	NR	NR	NR	NR	NR	NR	NR
	TOF 5 mg + cDMARD	376	NR	NR	NR	NR	NR	NR	NR	NR
	ADA + cDMARD	386	NR	NR	NR	NR	NR	NR	NR	NR

Study	Interventions	N	DAS28-CRP, n (%)		DAS28-ESR, n (%)		CDAI, n (%)		SDAI, n (%)	
			≤3.2	≤2.6	≤3.2	≤2.6	≤10	≤2.8	≤11	≤3.3
ORAL Standard[107] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	NR	NR	NR	NR	NR	NR	NR	NR
	ADA 40 mg + cDMARD	204	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo followed by TOF 5 mg + cDMARD	56	NR	NR	NR	NR	NR	NR	NR	NR
Nakamura 2018[103]	TOF group	22	NR	NR	NR	NR	NR	NR	NR	NR
	non-TNF group	20	NR	NR	NR	NR	NR	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1043	NR	NR	174 (16.6)†	77 (7.3)†	338 (32.4)†	67 (6.4)†	361 (34.6)†	67 (6.4)†
	bDMARD Naïve: cDMARD	638	NR	NR	29 (4.5)	15 (2.3)	92 (14.3)	5 (0.7)	91 (14.2)	5 (0.7)
	bDMARD-IR: TOF 5 mg	258	NR	NR	33 (12.7)§	17 (6.6)§	77 (29.5)‡	16 (5.9)§	77 (29.8)†	18 (6.8)
	bDMARD-IR: cDMARD	191	NR	NR	10 (5.1)	5 (2.3)	28 (14.4)	3 (1.2)	27 (13.8)	2 (0.6)
Kremer 2012[104]	TOF 5 mg + cDMARD	71	NR	12 (16.4)¶¶	NR	NR	NR	NR	NR	NR
	cDMARD	69	NR	5 (6.1)	NR	NR	NR	NR	NR	NR
Upadacitinib										
SELECT-MONOTHERAPY[10] [5] Smolen 2019	UPA 15 mg	217	97 (44.7)*	61 (28.1)*	54 (24.9)†	30 (13.8)†	76 (35.3)*	28 (12.9)*	80 (36.9)	30 (13.8)*
	UPA 30 mg	215	114 (53.0)*	88 (40.9)*	84 (39.1)†	30 (14.0)†	101 (47.0)*	41 (19.1)*	101 (47.0)*	39 (18.1)*
	cDMARD	216	41 (19.0)	17 (7.9)	22 (10.2)	1 (0.5)	54 (25.0)	2 (0.9)	52 (24.1)	2 (0.9)
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	293 (45.0)†§§	189 (29.0)†§§	NR	NR	260 (39.9)†§§	85 (13.1)†§§	260 (39.9)	78 (12.0)
	ADA 40 mg + cDMARD‡	327	95 (29.1)	59 (18.0)	NR	NR	98 (30.0)	26 (8.0)	98 (30.0)	23 (7.0)

Study	Interventions	N	DAS28-CRP, n (%)		DAS28-ESR, n (%)		CDAI, n (%)		SDAI, n (%)	
			≤3.2	≤2.6	≤3.2	≤2.6	≤10	≤2.8	≤11	≤3.3
	Placebo + cDMARD	651	91 (14.0)†	39 (6.0)†	NR	NR	104 (16.0)	20 (3.1)	98 (15.1)	20 (3.1)
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	71 (43.3)*	NR	NR	NR	53 (32.3)†	NR	56 (34.1)*	NR
	UPA 30 mg + cDMARD	165	69 (41.8)*	NR	NR	NR	56 (33.9)*	NR	58 (35.2)*	NR
	cDMARD	169	24 (14.2)	NR	NR	NR	24 (14.2)	NR	24 (14.2)	NR
SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	107 (48.4)*	68 (30.8)*	NR	NR	89 (40.3)*	20 (9.0)‡	92 (41.6)*	21 (9.5)‡
	UPA 30 mg + cDMARD	119	105 (47.9)*	62 (28.3)*	NR	NR	92 (42.0)*	26 (11.9)†	99 (45.2)*	27 (12.3)†
	cDMARD	221	38 (17.2)	22 (10.0)	NR	NR	42 (19.0)	7 (3.2)	42 (19.2)	7 (3.2)

ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, CDAI: clinical disease activity index, cDMARD: conventional disease-modifying antirheumatic drug, CRP: C-reactive protein, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, SDAI: simple disease activity index, n: number, N: total number, NR: not reported

*p<0.0001.

†p<0.001

‡p<0.01.

§p<0.05 vs. placebo.

§§p<0.001.

¶¶Data was digitized and should be interpreted with caution.

Table D9. Outcomes at Three Months (12-14 Weeks) – HAQ-DI, Sharp Score

Study	Interventions	N	Change in HAQ-DI, Mean (SD)	HAQ-DI Score Improvement, n (%)			SHARP Score (mTSS), n (%)		
				≥0.22	≥0.3	≥0.5	<0	<0.5	<SDC (1.2)
Baricitinib (BAR)									
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	-0.57 (NR)¶¶	158 (69.0)†	138 (60.0)†	NR	NR	NR	NR
	cDMARD	228	-0.36 (NR)¶¶	124 (54.0)	92 (44.0)	NR	NR	NR	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	-0.37 (NR)†¶¶	103 (59.0)‡	84 (48.0)§	NR	NR	NR	NR
	cDMARD	176	-0.18 (NR)¶¶	76 (43.0)	62 (35.0)	NR	NR	NR	NR
RA-BEYOND[96,97] (abstract) Genovese 2017, Van Der Heijde 2019	Continued BAR 4 mg	147	0.04 (0.26)	NR					
	Stepped down to BAR 2 mg	146	0.06 (0.28)						
Keystone 2015[98]	BAR 2 mg	52	−0.18 (NR)	NR	NR	NR	NR	NR	NR
	cDMARD	98	−0.10 (NR)	NR	NR	NR	NR	NR	NR
Tofacitinib (TOF)									
ORAL Sync[41,99] Kremer 2013, Strand 2017	TOF 5 mg	315	-0.44 (NR)†	NR	NR	NR	NR	NR	NR
	Placebo	159	-0.16 (NR)	NR	NR	NR	NR	NR	NR
ORAL Step[49,100] Burmester 2013, Strand 2015	TOF 5 mg	132	-0.43 (NR)*	71 (54.2)§	NR	47 (35.9)‡	NR	NR	NR
	Placebo	131	-0.18 (NR)	53 (40.5)	NR	27 (20.6)	NR	NR	NR
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	-0.4 (NR)	NR	NR	NR	NR	NR	NR
	Placebo advanced to TOF 5 mg (at 6 months)	81	-0.15 (NR)	NR	NR	NR	NR	NR	NR
ORAL Strategy[43,101] Fleischmann 2017 Strand 2017	TOF 5 mg	384	-0.47 (NR)¶¶	NR	NR	NR	NR	NR	NR
	TOF 5 mg + cDMARD	376	-0.54 (NR)¶¶	NR	NR	NR	NR	NR	NR
	ADA + cDMARD	386	-0.49 (NR)¶¶	NR	NR	NR	NR	NR	NR
ORAL Standard[107] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	-0.55 (NR)§¶¶	NR	NR	NR	NR	NR	NR
	ADA 40 mg + cDMARD	204	-0.49 (NR)§	NR	NR	NR	NR	NR	NR
	Placebo followed by TOF 5 mg + cDMARD	56	-0.24 (NR)	NR	NR	NR	NR	NR	NR

Study	Interventions	N	Change in HAQ-DI, Mean (SD)	HAQ-DI Score Improvement, n (%)			SHARP Score (mTSS), n (%)		
				≥0.22	≥0.3	≥0.5	<0	<0.5	<SDC (1.2)
Nakamura 2018[103]	TOF group	22	%-change: -36.2	NR	NR	NR	NR	NR	NR
	Non-TNF group	20	%-change: -28.1	NR	NR	NR	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD naïve: TOF 5 mg	1043	NR	552 (52.9)†	NR	421 (40.3)†	NR	NR	NR
	bDMARD naïve: cDMARD	638	NR	184 (28.7)	NR	117 (18.2)	NR	NR	NR
	bDMARD-IR: TOF 5 mg	258	NR	118 (45.7)	NR	80 (31.0)§	NR	NR	NR
	bDMARD-IR: cDMARD	191	NR	71 (36.9)	NR	39 (20.1)	NR	NR	NR
Kremer 2012[104]	TOF 5 mg + cDMARD	71	-0.49 (0.1)†	NR	NR	NR	NR	NR	NR
	cDMARD	69	-0.16 (0.1)	NR	NR	NR	NR	NR	NR
Upadacitinib (UPA)									
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	-0.65 (95% CI: -0.73, -0.57)†	140 (65.7)	NR	NR	NR	NR	NR
	UPA 30 mg	215	-0.73 (95% CI: -0.81, -0.64)†	148 (72.5)	NR	NR	NR	NR	NR
	cDMARD	216	-0.32 (95% CI: -0.41, -0.24)	98 (47.8)	NR	NR	NR	NR	NR
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	-0.6 (NR)†‖	NR	NR	NR	NR	NR	NR
	ADA 40 mg + cDMARD‡	327	-0.49 (NR)	NR	NR	NR	NR	NR	NR
	Placebo + cDMARD	651	-0.28 (NR)	NR	NR	NR	NR	NR	NR
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	-0.41 (95% CI -0.50 to -0.33)****	105 (64.1)****	NR	NR	NR	NR	NR
	UPA 30 mg + cDMARD	165	-0.44 (95% CI -0.52 to -0.35)****	92 (55.6)**	NR	NR	NR	NR	NR
	cDMARD	169	-0.16 (95% CI -0.25 to -0.08)	63 (37.4)	NR	NR	NR	NR	NR

Study	Interventions	N	Change in HAQ-DI, Mean (SD)	HAQ-DI Score Improvement, n (%)			SHARP Score (mTSS), n (%)		
				≥0.22	≥0.3	≥0.5	<0	<0.5	<SDC (1.2)
SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	-0.61 (NR)	156/212 (73.6)	NR	NR	NR	NR	NR
	UPA 30 mg + cDMARD	219	-0.55 (NR)	148/214 (69.2)	NR	NR	NR	NR	NR
	cDMARD	221	-0.26 (NR)	109/221 (49.3)	NR	NR	NR	NR	NR

ACR: American College of Rheumatology, ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, cDMARD: conventional disease-modifying antirheumatic drug, EULAR: European League Against Rheumatology, N/A: not available, n: number, N: total number, NR: not reported

*p<0.0001.

†p<0.001

‡p<0.01.

§p<0.05 vs. placebo.

§§p<0.001.

¶¶Data was digitized and should be interpreted with caution.

Table D10. Patient Reported Outcomes at Three Months (12-14 weeks) – Pain, Fatigue, and Quality of Life

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)
Baricitinib (BAR)												
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	-25.3¥¥	NR	-31.7¥¥	NR	-25.5¥¥	NR	NR	NR	NR	NR
	cDMARD	228	-16.8¥¥	NR	-22.0¥¥	NR	-15.6¥¥	NR	NR	NR	NR	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	-20.5¥¥	NR	-20.8¥¥	NR	-17.1¥¥	NR	NR	NR	NR	NR
	cDMARD	176	-8.9¥¥	NR	-17.1¥¥	NR	-8.7¥¥	NR	NR	NR	NR	NR
RA-BEYOND[96,97] Genovese 2017 (Abstract) Van Der Heijde 2019	Continued BAR 4 mg	147	1.2 (14.3)	NR	−0.0 (9.6)	NR	0.7 (14.7)	NR	NR	NR	NR	NR
	Stepped down to BAR 2 mg	146	2.5 (14.5)	NR	2.7 (13.6)††	NR	2.5 (16.4)	NR	NR	NR	NR	NR
Keystone 2015[98]	BAR 2 mg	52	−16.2 (NR)	NR	-25.0 (NR)	NR	−14.2 (NR)	NR	NR	NR	NR	NR
	cDMARD	98	−10.3 (NR)	NR	-19.0 (NR)	NR	−8.8 (NR)	NR	NR	NR	NR	NR
Tofacitinib (TOF)												
ORAL Sync[41,99] Kremer 2013 Strand 2017	TOF 5 mg	315	-24.8 (1.2)‡	216 (68.6)	NR	NR	-24.2 (1.2)‡	214 (67.9)	5.8 (0.5)‡	170 (53.7)	5.9 (0.4)/ 4.4 (0.5)	204 (64.5)/ 184 (58.4)
	Placebo (advanced to TOF 5 mg at 6 months)	79	-12.5 (1.7)	39 (49.3)	NR	NR	-11.4 (1.7)	37 (46.0)	2.1 (0.6)	33 (40.8)	2.4 (0.6) /1.6 (0.7)	38 (47.3) /33 (41.8)
ORAL Step[49,100] Burmester 2013 Strand 2015	TOF 5 mg	133	-23.4 (2.4)‡	87 (64.9)†	NR	NR	-27.2 (2.4)‡	93 (69.3)‡	6.3 (1.0)‡	82 (61.5)†	5.65 (0.68)‡/ 3.52 (0.92)§	91 (67.8)/ 72 (54.2)

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)
	Placebo‡‡	132	-9.2 (2.4)	56 (41.9)	NR	NR	-8.3 (2.4)	52 (39.1)	1.1 (1.0)	51 (38.60)	2.0 (0.7) /0.4 (0.9)	65 (49.1)/ 49 (37.1)
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	202	NR									
	Placebo	62										
ORAL Strategy[43,101] Fleischmann 2017 Strand 2017	TOF 5 mg	384	NR									
	TOF 5 mg + cDMARD	376										
	ADA + cDMARD	386										
ORAL Standard[102,107] Van Vollenhoven 2013 Strand 2016	TOF 5 mg + cDMARD	204	-23.8 (1.7)†	144 (70.3)†	NR	NR	-26.7 (1.6)†	142 (69.2)†	5.9 (0.6)	109 (53.2)§	7.0 (0.5)†/ 3.2 (0.7)	139 (67.9)§/ 102 (50.0)
	ADA 40 mg + cDMARD	204	-21.5 (1.7)†	132 (64.4)†	NR	NR	-22.5 (1.6)†	132 (64.4)†	5.0 (0.6)*	115 (56.0)*	6.3 (0.5)*/ 3.4 (0.7)	136 (66.3)§ /106 (51.9)
	Placebo followed by TOF 5 mg + cDMARD	56	-7.3 (2.3)	20 (35.4)	NR	NR	-9.5 (2.2)	23 (39.6)	1.6 (0.8)	20 (35.4)	3.2 (0.7) /1.8 (0.9)	29 (51.0)/ 24 (42.7)
Nakamura 2018[103]	TOF 5 mg	22	NR									
	Non-TNF biologics	20										
Charles-Schoeman 2016[38]	bDMARD naïve: TOF 5 mg	1071	NR									

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)
	bDMARD naïve: cDMARD	651										
	bDMARD-IR: TOF 5 mg	259										
	bDMARD-IR: cDMARD	193										
Kremer 2012[104]	TOF 5 mg + cDMARD	71	-33.8 (2.3)†	NR	-27.1 (2.7)§	NR	-27.4 (2.8)†	NR	NR	NR	NR	NR
	cDMARD	69	-22.8 (2.3)	NR	-15.1 (2.8)	NR	-13.0 (2.8)	NR	NR	NR	NR	NR
Upadacitinib (UPA)												
SELECT-MONOTHERAPY[105,106] Smolen 2019, Strand 2018	UPA 15 mg	217	-23.4 (95% CI: -27.1, -19.8)§	133 (61.0)	-39.8 (NR)	NR	-26.2 (95% CI: -29.7, -22.6)§	139 (64.0)	NR	NR	8.3 (95% CI: 7.2, 9.4)/ 4.6 (95% CI: 3.3, 5.8)§	141 (65.0) / 109 (50.0)
	UPA 30 mg	215	-29.9 (95% CI: -33.5, -26.3)§	160 (74.0)	-41.9 (NR)	NR	-33.2 (95% CI: -36.7, -29.7)§	162 (75.0)	NR	NR	10.2 (95% CI: 9.1, 11.3)/ 4.7 (95% CI: 3.5, 5.9)§	157 (73.0) / 125 (58.0)

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)
	cDMARD	216	-11.2 (95% CI: -14.9, -7.5)	102 (47.0)	-26.4 (NR)	NR	-13.9 (95% CI: -17.4, -10.3)	98 (45.0)	NR	NR	4.3 (95% CI: 3.2, 5.4)/ 1.9 (95% CI: 0.6, 3.1)	104 (48.0)/ 91 (42.0)
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	-31.0¥†¥¥	NR	-39.8¥†¥¥	NR	-32.1 (NR)†¥	NR	9.0 (NR)†§§	NR	7.9 (NR)†¶¶/ NR	NR
	ADA 40 mg + cDMARD	327	-24.1¥¥	NR	-37.3¥¥	NR	-25.6 (NR)	NR	7.4 (NR)	NR	6.3 (NR) /NR	NR
	Placebo + cDMARD	651	-15.8¥¥	NR	-25.1¥¥	NR	-15.7 (NR)	NR	4.8 (NR)	NR	3.6 (NR) /NR	NR
SELECT-BEYOND[48,106] Genovese 2018 Strand 2018	UPA 15 mg + cDMARD	164	-26.04 (95% CI: -30.16, -21.93)*	NR	-38.9¥¥	NR	-25.91 (95% CI: -30.05, -21.76)*	NR	NR	NR	5.83 (95% CI: 4.60, 7.05)*/ 4.54 (95% CI: 3.22, 5.87)	NR
	UPA 30 mg + cDMARD	165	-29.27 (95% CI: -33.43, -25.12)*	NR	-40.6¥¥	NR	-30.92 (95% CI: -35.12, -26.72)*	NR	NR	NR	7.02 (95% CI: 5.78, 8.25)*/ 3.37 (95% CI:	NR

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)
											2.03, 4.72)	
	Placebo + cDMARD	169	-10.03 (95% CI: -14.22, -5.84)	NR	-25.7¥¥	NR	-10.38 (95% CI: -14.60, -6.16)	NR	NR	NR	2.39 (95% CI: 1.14, 3.64)/ 3.01 (95% CI: 1.65, 4.51)	NR
SELECT-NEXT[40,106] Burmester 2018 Strand 2018	UPA 15 mg + cDMARD	221	-29.7‡ (95% CI: -33.2, -26.2)	157 (71.0)	-38.3 (NR)‡	NR	-29.9§ (95% CI: -33.4, -26.4)	162 (73.0)	7.9§ (95% CI: 6.6, 9.3)	142 (64.0)	7.6§ (95% CI: 6.4, 8.7) /4.7§ (95% CI: 3.4, 6.0)	153 (69.0) / 122 (55.0)
	UPA 30 mg + cDMARD	219	-30.5‡ (95% CI: -34.0, -27.0)	158 (72.0)	-40.2 (NR)‡	NR	-31.7§ (95% CI: -35.2, -28.2)	160 (73.0)	7.7§ (6.4, 9.1)	125 (57.0)	8.0§ (95% CI: 6.8, 9.2)/ 3.7 (95% CI: 2.4, 5.0)	154 (70.0)/ 99 (45.0)
	Placebo + cDMARD	221	-10.4 (95% CI: -13.8, -6.9)	95 (43.0)	-23.2 (NR)	NR	-10.3 (95% CI: -13.7, -6.8)	98 (44.0)	3.0 (95% CI: 1.6, 4.3)	91 (41.0)	3.0 (95% CI: 1.9, 4.2)	106 (48.0)/ 99 (41.0)

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID, n (%)
											/2.6 (95% CI: 1.3, 3.9)	

bDMARD: biologic disease modifying anti-rheumatic drug, cDMARD: conventional disease modifying anti-rheumatic drug, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, GA: Global Assessment, IR: inadequate response, LSM: least square mean, MCID: minimal clinically important difference, MCS: Mental Component Score, n: number, N: total number, N/A: not available, NR: not reported, PCS: Physical Component Score, SE: standard error, SF: Short Form, TNF: tumor necrosis factor, VAS: visual analogue scale

*p<0.01.

†p<0.001.

‡p<0.0001 vs. placebo.

§p<0.5.

§§p<0.5.

¶¶p<0.01.

¥p<0.001.

#p<0.0001 vs. adalimumab.

††p<0.05 vs. baricitinib.

‡‡Total placebo arm (advanced to either TOF 5mg or 10mg at 6 months).

¥¥Data are digitized and should be interpreted with caution.

Table D11. Outcomes at Six Months (24-26 Weeks) – ACR and EULAR

Study	Interventions	N	ACR20, n (%)	ACR50, n (%)	ACR70, n (%)	EULAR, n (%)
Baricitinib (BAR)						
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	140 (61.0)†	95 (41.0)†	58 (25.0)†	NR
	cDMARD	228	96 (42.0)	49 (21.0)	18 (8.0)	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	78 (45.0)†	40 (23.0)§	23 (13.0)†	NR
	cDMARD	176	48 (27.0)	23 (13.0)	6 (3.0)	NR
RA-BEYOND[96,97] (abstract) Genovese 2017, Van Der Heijde 2019	Continued BAR 4 mg	147	NR			
	Stepped down to BAR 2 mg	146				
Keystone 2015[98]	BAR 2 mg	52	N/A			
	cDMARD	98	N/A			
Tofacitinib (TOF)						
ORAL Sync[41] Kremer 2013	TOF 5 mg	315	164 (52.1)†	105 (33.4)†	41 (12.4)†	NR
	Placebo (advanced to TOF 5 mg at 6 months)	159	49 (30.8)	20 (12.4)†	5 (.03)§	NR
ORAL Step[49] Burmester 2013	TOF 5 mg	133	N/A			
	Placebo (advanced to TOF 5 mg at 3 months)	132				
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	81 (51.5)†	103 (32.4)†	45 (14.6)†	NR
	Placebo (advanced to TOF 5 mg at 6 months)	81	21 (25.3)	7 (8.4)	1 (1.3)	NR
ORAL Strategy[43] Fleischmann 2017	TOF 5mg	384	249 (65.0)	147 (38.0)	70 (18.0)	NR
	TOF 5 mg + cDMARD	376	275 (73.0)	173 (46.0)	94 (25.0)	NR
	ADA + cDMARD	386	274 (71.0)	169 (44.0)	80 (21.0)	NR
ORAL Standard[107] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	101/196 (51.5)	77 (37.6)¶¶¥	41 (20.0)¶¶¥	NR
	ADA +cDMARD 40 mg	204	94/199 (47.2)	58 (28.2)¶¶¥	19 (9.0)¶¶¥	
	Placebo followed by TOF 5 mg + cDMARD	56	30/106 (28.3)	8 (13.2)¶¶¥	2 (2.3)¶¶¥	NR
Nakamura 2018[103]	TOF 5 mg	22	NR	NR	NR	NR
	Non-TNF	20	NR	NR	NR	NR
	bDMARD Naïve: TOF 5 mg	1071	557 (51.9)	354 (32.9)	161 (15.0)	NR

Charles-Schoeman 2016[38]	bDMARD Naïve: cDMARD	651	NR	NR	NR	NR
	bDMARD-IR: TOF 5 mg	259	117 (45.6)	83 (32.0)	37 (14.8)	NR
	bDMARD-IR: cDMARD	193	NR	NR	NR	NR
Kremer 2012[104]	TOF 5 mg	71	35 (49.0)	24 (33.2)	14 (18.9)§	NR
	Placebo	69	25 (35.3)	16 (22.9)	5 (6.9)§	NR
Upadacitinib (UPA)						
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	N/A			
	UPA 30 mg	215				
	cDMARD	216				
SELECT-COMPARE[39] Fleishmann 2019	UPA 15 mg + cDMARD	651	436 (67.0)†§§	352 (54.1)†§§	NR	NR
	ADA + cDMARD#	327	186 (56.9)	137 (41.9)	NR	NR
	Placebo + cDMARD	651	234 (35.9)	137 (21.0)	NR	NR
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	105 (63.6)¶¶	70 (42.5) ¶¶	37 (22.1) ¶¶	N/A
	UPA 30 mg + cDMARD	165	99 (59.7)¶¶	73 (43.7) ¶¶	40 (24.2) ¶¶	
	Placebo + cDMARD	169	N/A			
SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	N/A			
	UPA 30 mg + cDMARD	219				
	cDMARD	221				

ACR: American College of Rheumatology, ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, cDMARD: conventional disease-modifying antirheumatic drug, EULAR: European League Against Rheumatology, N/A: not available, n: number, N: total number, NR: not reported

*p<0.0001.

†p<0.001

‡p<0.01.

§p<0.05 vs. placebo.

§§p<0.001.

¶¶Data was digitized and should be interpreted with caution.

¥With advanced placement therapy.

Table D12. Outcomes at Six Months (24-26 Weeks) – DAS28, SDAI, CDAI

Study	Interventions	N	DAS28-CRP, n (%)		DAS28-ESR, n (%)		CDAI, n (%)		SDAI, n (%)	
			≤3.2	≤2.6	≤3.2	≤2.6	≤10	≤2.8	≤11	≤3.3
Baricitinib (BAR)										
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	106 (46.0)†	71 (31.0)†	67 (29.0)†	33 (14.0)†	104 (45.0)‡	35 (15.0)†	110 (48.0)‡	39 (17.0)†
	cDMARD	228	55 (24.0)	26 (11.0)	23 (10.0)	10 (4.0)	64 (28.0)	10 (4.0)	46 (29.0)	10 (4.0)
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	35 (20.0)§	20 (11.0)	21 (12.0)	9 (5.0)	41 (23.0)	9 (5.0)	39 (22.0)§	9 (5.0)
	cDMARD	176	20 (11.0)	11 (6.0)	13 (7.0)	6 (3.0)	27 (15.0)	6 (3.0)	25 (14.0)	4 (2.0)
RA-BEYOND[96,97] Genovese 2017 (Abstract) Van Der Heijde 2019	Continued BAR 4 mg	147	NR							
	Stepped down to BAR 2 mg	146								
Keystone 2015[98]	BAR 2 mg	52	N/A							
	cDMARD	98								
Tofacitinib (TOF)										
ORAL Sync[41] Kremer 2013	TOF 5 mg	315	NR	NR	NR	24 (8.5)	NR	NR	NR	NR
	Placebo (advanced to TOF 5 mg at 6 months)	159	NR	NR	NR	4 (2.6)	NR	NR	NR	NR
ORAL Step[49] Burmester 2013	TOF 5mg	122	N/A							
	Placebo (advanced to TOF 5 mg at 3 months)	66								
ORAL Scan[44] Van der Heijde 2013	TOF 5mg	321	NR	NR	45 (14.3)†	225 (7.2)	NR	NR	NR	NR
	Placebo (advanced to TOF 5 mg	81	NR	NR	3 (3.1)	2 (1.6)	NR	NR	NR	NR

Study	Interventions	N	DAS28-CRP, n (%)		DAS28-ESR, n (%)		CDAI, n (%)		SDAI, n (%)	
			≤3.2	≤2.6	≤3.2	≤2.6	≤10	≤2.8	≤11	≤3.3
	at 6 months)									
ORAL Strategy[43] Fleishmann 2017	TOF 5 mg	384	159 (41)	81 (21)	79 (21)	40 (10)	163 (42)	39 (10)	167 (43)	38 (10)
	TOF 5 mg + cDMARD	376	174 (46)	115 (31)	100 (27)	45 (12)	183 (49)	52 (14)	187 (50)	50 (13)
	ADA + cDMARD	386	181 (47)	108 (28)	106 (27)	48 (12)	179 (46)	51 (13)	182 (47)	50 (13)
ORAL Standard[42] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	NR	NR	NR	11/177 (6.2)	NR	NR	NR	NR
	ADA 40 mg + cDMARD	204	NR	NR	NR	12/178 (6.7)	NR	NR	NR	NR
	Placebo followed by TOF 5 mg + cDMARD	56	NR	NR	NR	1/92 (1.1)	NR	NR	NR	NR
Nakamura 2018[103]	TOF 5 mg	22	NR	NR	NR	NR	NR	NR	NR	NR
	Non-TNF	20	NR	NR	NR	NR	NR	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD naïve: TOF 5 mg	1071	NR	NR	172 (16.3)	750 (7.2)	NR	NR	NR	NR
	bDMARD naïve: cDMARD	651	NR	NR	NR	NR	NR	NR	NR	NR
	bDMARD-IR: TOF 5 mg	259	NR	NR	47 (18.3)	19 (7.1)	NR	NR	NR	NR
	bDMARD-IR: cDMARD	193	NR	NR	NR	NR	NR	NR	NR	NR
Kremer 2012[104]	TOF 5 mg	71	2 (3.00)	21 (28.89)	NR	NR	NR	NR	NR	NR
	cDMARD	69	3 (3.45)	7 (10.31)	NR	NR	NR	NR	NR	NR
Upadacitinib (UPA)										
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	N/A							
	UPA 30 mg	215								
	cDMARD	216								
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	358 (55.0)†§§	267 (41.0)†§§	NR	NR	345 (53.0)†§§	150 (23.0)†§§	NR	NR
	ADA + cDMARD	327	128 (39.1)	88 (26.9)	NR	NR	124 (37.9)	46 (14.1)	NR	NR

Study	Interventions	N	DAS28-CRP, n (%)		DAS28-ESR, n (%)		CDAI, n (%)		SDAI, n (%)	
			≤3.2	≤2.6	≤3.2	≤2.6	≤10	≤2.8	≤11	≤3.3
	Placebo + cDMARD	651	117 (18.0)	59 (9.1)	NR	NR	143 (22.0)	39 (6.0)	NR	NR
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	86 (52.0)	NR		NR	NR	77 (47.0)	NR	81 (49.0)	N/A
	UPA 30 mg + cDMARD	86 (52.0)	NR		NR	NR	73 (44.0)	NR	75 (45.0)	
	Placebo + cDMARD	N/A								
SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221221	N/A							
	UPA 30 mg + cDMARD	219219								
	cDMARD	221221								

ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, CDAI: clinical disease activity index, cDMARD: conventional disease-modifying antirheumatic drug, CRP: C-reactive protein, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, N/A: not available, n: number, N: total number, NR: not reported, SDAI: simple disease activity index

†p<0.001.

‡p<0.01.

§p<0.05 vs. placebo.

§§p<0.001.

Table D13. Outcomes at Six Months (24-26 Weeks) – HAQ-DI, SHARP Score

Study	Interventions	N	Change in HAQ-DI, Mean (SD)	HAQ-DI Improvement, n (%)			Sharp Score, n (%)		
				≥0.22	≥0.3	≥0.5	<0	<0.5	<SDC (1.2)
Baricitinib (BAR)									
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	-0.4 (NR)§§	147 (64.0)‡	133 (58.0)‡	NR	163 (71.6)	187 (81.7	198 (86.5)
	cDMARD	228	-0.6 (NR)§§	96 (42.0)	85 (37.0)	NR	169 (74.2)	177 (77.4)	190 (83.2)
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	-0.2 (NR)§§	87 (50.0)†	72 (41.0)‡	NR	NR	NR	NR
	cDMARD	176	-0.4 (NR)§§	53 (30.0)	43 (24.0)	NR	NR	NR	NR
RA-BEYOND[96,97] Genovese 2017 (Abstract), Van Der Heijde 2019	Continued BAR 4 mg	147	NR						
	Stepped down to BAR 2 mg	146							
Keystone 2015[98]	BAR 2 mg	N/A							
	cDMARD								
Tofacitinib (TOF)									
ORAL Sync[41,99] Kremer 2013, Strand 2017	TOF 5 mg	315	208	NR	NR	NR	NR	NR	NR
	Placebo (advanced to TOF 5 mg at 6 months)	159	NR	NR	NR	NR	NR	NR	NR
ORAL Step[49,100] Burmester 2013, Strand 2015	TOF 5 mg	N/A							
	Placebo (advanced to TOF 5 mg at 3 months)								
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	-0.49 (NR)‡§§	NR	NR	NR	NR	285 (88.9)	NR
	Placebo (advanced to TOF 5 mg at 6 months)	81	-0.16 (NR)	NR	NR	NR	NR	63 (77.7)	NR
ORAL Strategy[43,101] Fleischmann 2017, Strand 2017	TOF 5 mg	384	-0.51 (NR)	NR	NR	NR	NR	NR	NR
	TOF 5 mg + cDMARD	376	-0.58 (NR)	NR	NR	NR	NR	NR	NR
	ADA + cDMARD	386	-0.54 (NR)	NR	NR	NR	NR	NR	NR
ORAL Standard[42] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	-0.63 (NR)	NR	NR	NR	NR	NR	NR
	ADA 40 mg + cDMARD	204	-0.55 (NR)	NR	NR	NR	NR	NR	NR
	Placebo followed by TOF 5 mg + cDMARD	56	-0.47 (NR)	NR	NR	NR	NR	NR	NR
Nakamura 2018[103]	TOF 5 mg	22	NR	NR	NR	NR	NR	NR	NR

Study	Interventions	N	Change in HAQ-DI, Mean (SD)	HAQ-DI Improvement, n (%)			Sharp Score, n (%)		
				≥0.22	≥0.3	≥0.5	<0	<0.5	<SDC (1.2)
	Non-TNF	20	NR	NR	NR	NR	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1071	NR	585 (54.6)	NR	447 (41.7)	NR	NR	NR
	bDMARD Naïve: cDMARD	651	NR	NR	NR	NR	NR	NR	NR
	bDMARD-IR: TOF 5 mg	259	NR	123 (47.4)	NR	87 (33.5)	NR	NR	NR
	bDMARD-IR: cDMARD	193	NR	NR	NR	NR	NR	NR	NR
Kremer 2012[104]	TOF 5 mg	71	-0.61 (NR)	NR	NR	NR	NR	NR	NR
	Placebo	69	-0.37 (NR)	NR	NR	NR	NR	NR	NR
Upadacitinib (UPA)									
SELECT-MONOTHERAPY[105] Smolen 2019	UPA 15 mg	217	N/A						
	UPA 30 mg	215							
	cDMARD	216							
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	NR	NR	NR	NR	NR	NR	NR
	ADA + cDMARD‡	327	NR	NR	NR	NR	NR	NR	NR
	Placebo + cDMARD	651	NR	NR	NR	NR	NR	NR	NR
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	-0.44§§		104 (63.2) §§	NR	NR	NR	NR	N/A
	UPA 30 mg + cDMARD	-0.53§§		95 (57.6) §§	NR	NR	NR	NR	
	Placebo + cDMARD	N/A							
SELECT-NEXT[40] Burmester 2018	UPA 15 mg + cDMARD	221	N/A						
	UPA 30 mg + cDMARD	219							
	cDMARD	221							

ADA: adalimumab, bDMARD: biologic disease-modifying antirheumatic drug, cDMARD: conventional disease-modifying antirheumatic drug, CRP: C-reactive protein, DAS: Disease Activity Score, ESR: erythrocyte sedimentation rate, HAQ: Health Assessment Questionnaire, mg: milligram, N/A: not available, n: number, N: total number, NR: not reported, SD: standard deviation, TNF: tumor necrosis factor

*p<0.5.

†p<0.01.

‡p<0.001.

§p<0.0001 vs. placebo.

§§Data are digitized and should be interpreted with caution.

Table D14. Patient Reported Outcomes at Six Months

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)
Baricitinib (BAR)												
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	-27.5***†	NR	-36.4 ***†	NR	-27.4 ***†	NR	NR	NR	NR	NR
	cDMARD	228	-18.8†	NR	-26.3†	NR	-19.7†	NR	NR	NR	NR	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	-20.3***†	NR	-28.9 ***†	NR	-18.7 ***†	NR	NR	NR	NR	NR
	cDMARD	176	-8.7†	NR	-19.7†	NR	-8.8†	NR	NR	NR	NR	NR
RA-BEYOND[96,97] Genovese 2017 (Abstract) Van Der Heijde 2019	Continued BAR 4 mg	147	NR									
	Stepped down to BAR 2 mg	146										
Keystone 2015[98]	BAR 2 mg	N/A										
	cDMARD											
Tofacitinib (TOF)												
ORAL Sync[41,99] Kremer 2013 Strand 2017	TOF 5 mg	315	-27.8†	NR	NR	NR	-28.9†	NR	NR	NR	5.7† /4.1†	NR
	Placebo (advanced to TOF 5 mg at 6 months)	79	-20.1†	NR	NR	NR	-19.5†	NR	NR	NR	7.4† /2.3†	NR
ORAL Step[49,100] Burmester 2013 Strand 2015	TOF 5 mg	N/A										
	Placebo¥											
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg	321	-25.8 (1.4)***	NR	-34.4 (1.2)***	NR	-26.4 (1.4)**	NR	NR	NR	NR	NR

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)
	Placebo (advanced to TOF 5 mg at 6 months)	81	-13.6 (2.4)	NR	-23.8 (2.0)	NR	-15.7 (2.4)	NR	NR	NR	NR	NR
ORAL Strategy[43,101] Fleischmann 2017 Strand 2017	TOF 5 mg	384	-35.7 (1.0)	NR	NR	NR	-26.6 (1.3)	NR	7.1 (0.5)	NR	6.7 (0.4) /5.2 (0.5)	NR
	TOF 5 mg + cDMARD	376	-38.4 (1.0)¤	NR	NR	NR	-30.7 (1.3)¤	NR	7.36 (0.5)¥	NR	7.9 (0.4) /5.7 (0.5)¤	NR
	ADA + cDMARD	386	-38.8 (1.0)¤	NR	NR	NR	-28.1 (1.3)	NR	6.1 (0.5)	NR	7.8 (0.4) /4.4 (0.5)	NR
ORAL Standard[42,102] Van Vollenhoven 2013 Strand 2016	TOF 5 mg + cDMARD	204	-28.6****†	NR	NR	NR	-30.6 ****†	NR	6.8 ****†	NR	8.5****† /5.3†	NR
	ADA 40 mg + cDMARD	204	-25.8****†	NR	NR	NR	-27.1 ****†	NR	6.5***†	NR	7.3***† /3.9†	NR
	Placebo followed by TOF 5 mg + cDMARD	56	-12.5†	NR	NR	NR	-16.0†	NR	2.1†	NR	4.1† /0.8†	NR
Nakamura 2018[103]	TOF 5 mg	22	NR									
	Non-TNF biologics	20										
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1071	NR									

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)
	bDMARD Naïve: cDMARD	651										
	bDMARD-IR: TOF 5 mg	259										
	bDMARD-IR: cDMARD	193										
Kremer 2012[104]	TOF 5 mg + cDMARD	71	NR									
	cDMARD	69										
Upadacitinib (UPA)												
SELECT-MONOTHERAPY[105,106] Smolen 2019 Strand 2018	UPA 15 mg	217	N/A									
	UPA 30 mg	215										
	cDMARD	216										
SELECT-COMPARE[39] Fleischmann 2019	UPA 15 mg + cDMARD	651	-35.7†	NR	-46.1†	NR	-36.5†	NR	9.7 (NR) ***#	NR	9.5 (NR) ***##/ NR	NR
	ADA 40 mg + cDMARD	327	-30.1†	NR	-41.4†	NR	-32.4†	NR	8.2 (NR)	NR	7.8 (NR) /NR	NR
	Placebo + cDMARD	651	-18.0†	NR	-27.6†	NR	-18.9†	NR	5.5 (NR)	NR	4.5 (NR) /NR	NR
SELECT-BEYOND[48,106] Genovese 2018 Strand 2018	UPA 15 mg + cDMARD	164	7.2 (NR) /NR									N/A
	UPA 30 mg + cDMARD	165	8.0 (NR) /NR									

Study	Intervention	N	Patients' GA, 0-100 mm VAS (SD)		Physicians' GA, 0-100 mm VAS (SD)		Pain, 0-100 mm VAS (SD)		FACIT-F		SF-36 (PCS / MCS)	
			Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)	Change from Baseline, LSM (SE)	Patients Reporting ≥MCID (%)
	Placebo + cDMARD	169										
SELECT-NEXT[40,106] Burmester 2018 Strand 2018	UPA 15 mg + cDMARD	221	N/A									
	UPA 30 mg + cDMARD	219										
	Placebo + cDMARD	221										

bDMARD: biologic disease modifying anti-rheumatic drug, cDMARD: conventional disease modifying anti-rheumatic drug, FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue, GA: Global Assessment, IR: inadequate response, LSM: least square mean, MCID: minimal clinically important difference, MCS: Mental Component Score, n: number, N: total number, N/A: not available, NR: not reported, PCS: Physical Component Score, SE: standard error, SF: Short Form, TNF: tumor necrosis factor, VAS: visual analogue scale

*p<0.5, **p<0.01, ***p<0.001, ****p<0.0001 vs. placebo, #p<0.5, ##p<0.01, ###p<0.001, ####p<0.0001 vs. adalimumab, ‡p<0,05 vs. baricitinib, ¥Total placebo arm (advanced to either TOF 5 mg or 10 mg at 6 months), †Data are digitized and should be interpreted with caution, ¤p<0.05 vs. tofacitinib mono therapy.

Table D15. Harms I

Study	Intervention	N	Time Point (Weeks)	Any Adverse Event, n (%)	Serious Adverse Event, n (%)	Adverse Event Leading to Discontinuation, n (%)	Nausea, n (%)	Nasopharyngitis, n (%)	Venous Thromboembolism, n (%)
Baricitinib (BAR)									
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	0-12	122 (53.0)	4 (2.0)	7 (3.0)	NR	NR	NR
	cDMARD	228	0-12	133 (58.0)	8 (4.0)	8 (4.0)	NR	NR	NR
	BAR 2 mg + cDMARD	229	0-24	154 (67.0)	6 (3.0)	10 (4.0)	7 (3.0)	10 (4.0)	NR
	cDMARD	228	0-24	161 (71.0)	11 (5.0)	10 (4.0)	8 (4.0)	18 (8.0)	NR
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	0-12	107 (61.0)	3 (2.0)	7 (4.0)	NR	NR	NR
	cDMARD	176	0-12	96 (55.0)	7 (4.0)	4 (2.0)	NR	NR	NR
	BAR 2 mg + cDMARD	174	0-24	123 (71.0)	7 (4.0)	7 (4.0)	7 (4.0)	12 (7.0)	NR
	cDMARD	176	0-24	112 (64.0)	13 (7.0)	7 (4.0)	5 (3.0)	7 (4.0)	NR
RA-BEYOND[96,97] (abstract) Genovese 2017 Van Der Heijde 2019	Continued BAR 4 mg	147	12	NR					
	Stepped down to BAR 2 mg	146	12						
Keystone 2015[98]	BAR 2 mg	52	0-12	TEAE: 24 (46.0)	3 (6.0)	5 (5.0)	NR	NR	NR
	cDMARD	98	0-12	TEAE: 45 (46.0)	3 (3.0)	1 (2.0)	NR	NR	NR
	BAR 2 mg	52	0-24	TEAE: 31 (60.0)	3 (6.0)	1 (2.0)	NR	NR	NR
	cDMARD	98	0-24	N/A					
Tofacitinib (TOF)									
ORAL Sync[41] Kremer 2013	TOF 5 mg + cDMARD	388	52	171.9 (152.5-193.8)	6.9 (4.6-10.5)	6.2 (4.0-9.6)	18 (5.5)	23 (7.1)	NR
	Placebo (advanced to TOF 5 mg at 6 months)	159	52	342.3 (281.1-416.9)	10.9 (4.9-24.2)	5.4 (1.8-16.8)	5 (9.0)	12 (21.6)	NR

Study	Intervention	N	Time Point (Weeks)	Any Adverse Event, n (%)	Serious Adverse Event, n (%)	Adverse Event Leading to Discontinuation, n (%)	Nausea, n (%)	Nasopharyngitis, n (%)	Venous Thromboembolism, n (%)
ORAL Step[49] Burmester 2013	TOF 5 mg + cDMARD	133	0-12	71 (53.4)	2 (1.5)	8 (6.0)	4 (3.0)	5 (3.8)	NR
	Placebo (advanced to TOF 5 mg)	132	0-12	75 (56.8)	6 (4.5)	7 (5.3)	9 (6.8)	4 (3.0)	NR
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg + cDMARD	321	12	TEAE: 157 (48.9)	12 (3.7)	15 (4.7)	7 (2.2)	14.4 (4.4)	NR
	Placebo (advanced to TOF 5 mg at 6 months)	160	12	TEAE: 73 (45.6)	5 (3.1)	5 (3.1)	2 (1.3)	1 (0.6)	NR
ORAL Strategy[43] Fleischmann 2017	TOF 5 mg	384	52	226 (59)	35 (9)	23 (6)	11 (3)	22 (6)	NR
	TOF 5 mg + cDMARD	376	52	231 (61)	27 (7)	26 (7)	13 (4)	16 (4)	NR
	ADA + cDMARD	386	52	253 (66)	24 (6)	37 (10)	16 (4)	18 (5)	NR
ORAL Standard[42] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	0-12	135 (66.2)	12 (5.9)	14 (6.9)	3 (1.5)	8 (3.9)	NR
	ADA 40 mg + cDMARD	204	0-12	105 (51.5)	5 (2.5)	10 (4.9)	3 (1.5)	7 (3.4)	NR
	Placebo followed by TOF 5 mg + cDMARD	56	0-12	57(52.8)	2 (1.9)	3 (2.8)	0	0 (0)	NR
Nakamura 2018[103]	TOF 5 mg	22	NR	NR	NR	3(12)	NR	NR	NR
	non-TNF biologics	20	NR	NR	NR	NR	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD naïve: TOF 5 mg	1071	0-24	NR	131 (12.2)	96 (9.1)	NR	NR	NR
	bDMARD naïve: cDMARD	651	0-6	NR	98 (15.0)	66 (10.1)	NR	NR	NR
	bDMARD-IR: TOF 5 mg	259	0-24	NR	34 (13.0)	39 (14.8)	NR	NR	NR
	bDMARD-IR: cDMARD	193	0-6	NR	37 (19.0)	37 (18.9)	NR	NR	NR
Kremer 2012[104]	TOF 5 mg	71	24	47 (66.2)	4(5.6)	3(4.2)	3(4.2)	5(7.0)	NR
	Placebo	51	24	29 (56.9)	0 (0)	3 (5.9)	1(1.4)	2(2.5)	NR
Upadacitinib (UPA)									
	UPA 15 mg	217	14	103 (47.5)	11 (5.0)	8 (3.7)	NR	NR	1 (<1)*
	UPA 30 mg	215	14	105 (48.8)	6 (2.8)	6 (2.8)	NR	NR	0 (0)

Study	Intervention	N	Time Point (Weeks)	Any Adverse Event, n (%)	Serious Adverse Event, n (%)	Adverse Event Leading to Discontinuation, n (%)	Nausea, n (%)	Nasopharyngitis, n (%)	Venous Thromboembolism, n (%)
SELECT-MONOTHERAPY[105] Smolen, 2019	cDMARD	216	14	102 (47.2)	6 (2.8)	6 (2.8)	NR	NR	0 (0)
SELECT-COMPARE[39] Fleischmann, 2018	UPA 15 mg + cDMARD	651	26	417 (64.2)	24 (3.7)	23 (3.5)	NR	NR	All*: 2 (0.3); PE: 1(0.2); DVT: 1 (0.2)
	ADA 40 mg + cDMARD	327	26	197 (60.2)	14 (4.3)	20 (6.1)	NR	NR	All*: 3 (0.9); PE: 3 (0.9); DVT: 0 (0)
	PBO + cDMARD	651	26	347 (53.2)	19 (2.9)	15 (2.3)	NR	NR	All*: 1 (0.2); PE: 1 (0.2); DVT: 0 (0)
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	12	91 (55.4)	8 (4.9)	4 (2.4)	NR	NR	PE: 1 (0.6)
	UPA 30 mg + cDMARD	165	12	111 (67.3)	12 (7.3)	15 (9.1)	NR	NR	0 (0)
	Placebo + cDMARD	169	12	95 (56.2)	0 (0)	9 (5.3)	NR	NR	0 (0)
SELECT-NEXT[40] Burmester, 2018	UPA 15 mg + cDMARD	221	12	125 (56.6)	9 (4.1)	7 (3.2)	16 (7.2)	12 (5.4)	0 (0)
	UPA 30 mg + cDMARD	219	12	118 (53.9)	6 (2.7)	13 (5.9)	3 (1.4)	13 (5.9)	0 (0)
	cDMARD	221	12	108 (48.9)	5 (2.3)	7 (3.2)	7 (3.2)	9 (4.1)	0 (0)

N/A: not available, n: number, N: total number, NR: not reported, TEAE: treatment emergent adverse event

*(Adjudicated) pulmonary embolism deemed unrelated to study drug.

Table D16. Harms II

Study	Intervention	N	Time Point (Weeks)	Upper Resp. Infection, n (%)	Malignancy, n (%)	Death, n (%)	Headache, n (%)	Infections, n (%)			
								Serious	Opportunistic	Herpes Zoster Virus	TB
Baricitinib (BAR)											
RA-BUILD[95] Dougados 2017	BAR 2 mg + cDMARD	229	0-12	NR	0 (0)	0 (0)	NR	1 (<1)	45 (20.0)	3 (1.0)	0 (0)
	cDMARD	228	0-12	NR	0 (0)	2 (0.9)	NR	3 (1.0)	53 (23.0)	0 (0)	0 (0)
	BAR 2 mg + cDMARD	229	0-24	14 (6.0)	0 (0)	0 (0)	15 (7.0)	2 (<1)	70 (31.0)	4 (2.0)	0 (0)
	cDMARD	228	0-24	18 (8.0)	0 (0)	2 (0.9)	8 (4.0)	4 (2.0)	79 (35.0)	0 (0)	0 (0)
RA-BEACON[50] Genovese 2016	BAR 2 mg + cDMARD	174	0-12	NR	NR	0 (0)	NR	3 (2)	61 (35.0)	2 (1.0)	NR
	cDMARD	176	0-12	NR	NR	0 (0)	NR	3 (2)	35 (20.0)	1 (<1)	NR
	BAR 2 mg + cDMARD	174	0-24	16 (9.0)	NR	0 (0)	17 (10.0)	4 (2)	76 (44.0)	2 (1.0)	NR
	cDMARD	176	0-24	8 (5.0)	NR	0 (0)	11 (6.0)	5 (3)	55 (31.0)	2 (1.0)	NR
RA-BEYOND[96,97] (abstract) Genovese 2017 Van Der Heijde 2019	Continued BAR 4 mg	147	0-12	NR							
	Stepped down to BAR 2 mg	146	0-12								
Keystone 2015[98]	BAR 2 mg	52	0-12	NR	NR	NR	NR	NR	NR	NR	NR
	cDMARD	98	0-12	NR	NR	NR	NR	NR	NR	NR	NR
	BAR 2 mg	52	0-24	NR	NR	NR	NR	NR	NR	NR	NR
	cDMARD	98	N/A								
Tofacitinib (TOF)											
ORAL Sync[41] Kremer 2013	TOF 5 mg + cDMARD	315	52	40 (12.3)	NR	NR	16 (4.9)	NR	NR	9 (4.2) MTX w/o leflunomide	NR
	Placebo (advanced to TOF 5 mg at 6 months)	79	52	7 (12.6)	NR	NR	8 (14.4)	NR	NR	2 (6.8) MTX alone	NR
ORAL Step[49] Burmester 2013	TOF 5 mg + cDMARD	133	0-12	5 (3.8)	NR	0 (0)	3 (2.3)	0 (0)	0 (0)	NR	NR
	Placebo	132	0-12	4 (3.0)	NR	0 (0)	1 (0.8)	0 (0)	0 (0)	NR	NR

Study	Intervention	N	Time Point (Weeks)	Upper Resp. Infection, n (%)	Malignancy, n (%)	Death, n (%)	Headache, n (%)	Infections, n (%)			
								Serious	Opportunistic	Herpes Zoster Virus	TB
	(advanced to TOF 5 mg)										
ORAL Scan[44] Van der Heijde 2013	TOF 5 mg + cDMARD	321	0-12	9 (2.8)	NR	2 (0.6)	18 (5.6)	2 (0.6)	NR	3 (0.9)	NR
	Placebo (advanced to TOF 5 mg at 6 months)	160	0-12	5 (3.1)	NR	0 (0)	3 (1.9)	0 (0)	NR	0 (0)	NR
ORAL Strategy[43] Fleischmann 2017	TOF 5 mg	384	52	25 (7)	1 (<1)	2 (1)	NR	6 (2)	2 (1)	1/69 (1)	0 (0)
	TOF 5 mg + cDMARD	376	52	37 (10)	0 (0)	0 (0)	NR	10 (3)	1 (<1)	2/75 (3)	2 (1)
	ADA + cDMARD	386	52	29 (8)	0 (0)	0 (0)	NR	6 (2)	2 (1)	0/27 (0)	0 (0)
ORAL Standard[42] Van Vollenhoven 2013	TOF 5 mg + cDMARD	204	12	9 (4.4)	NR	1 (<1)	8 (3.9)	3(1.5)	NR	0 (0)	NR
	ADA 40 mg + cDMARD	204	12	7 (3.4)	NR	1 (<1)	5 (2.5)	0 (0)	NR	0 (0)	NR
	Placebo followed by TOF 5 mg + cDMARD	56	12	1 (0.9)	NR	NR	2 (1.9)	1(0.9)	NR	0 (0)	NR
Nakamura 2018[103]	TOF 5 mg	22	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Non-TNF biologics	20	NR	NR	NR	NR	NR	NR	NR	NR	NR
Charles-Schoeman 2016[38]	bDMARD Naïve: TOF 5 mg	1071	0-24	NR	NR	7 (0.6)	NR	32 (3.4)	NR	43 (4.0)	0 (0)
	bDMARD Naïve: cDMARD	651	0-6	NR	NR	5 (0.7)	NR	13 (2.0)	NR	13 (2.0)	0 (0)
	bDMARD-IR: TOF 5 mg	259	0-24	NR	NR	1(1.2)	NR	6 (2.3)	NR	5.4	0 (0)
	bDMARD-IR: cDMARD	193	0-6	NR	NR	0 (0)	NR	0 (0)	NR	0 (0)	0 (0)
Kremer 2012[104]	TOF 5 mg	71	0-24	5(7.0)	NR	0 (0)	2(2.8)	1(1.4)	16 (22.5)*	NR	NR
	Placebo	69	0-12	2(2.9)	NR	0 (0)	1(1.4)	0 (0)	3 (5.9)*	NR	NR
Upadacitinib (UPA)											
	UPA 15 mg	217	14	NR	2 (0.9)	1 (0.5)	NR	1 (0.5)	0 (0)	3 (1.4)	0 (0)

Study	Intervention	N	Time Point (Weeks)	Upper Resp. Infection, n (%)	Malignancy, n (%)	Death, n (%)	Headache, n (%)	Infections, n (%)			
								Serious	Opportunistic	Herpes Zoster Virus	TB
SELECT-MONTHERAPY[105] Smolen, 2019	UPA 30 mg	215	14	NR	0 (0)	0 (0)	NR	0	3 (1.4)	6 (2.8)	0 (0)
	cDMARD	216	14	NR	1 (0.5)	0 (0)	NR	1 (0.5)	1 (0.5)	1 (0.5)	0 (0)
SELECT-COMPARE[39] Fleischmann, 2018	UPA 15 mg + cDMARD	651	26	NR	0 (0)	0 (0)	NR	12 (1.8)	4 (0.6)	5 (0.8)	NR
	ADA 40 mg + cDMARD	327	26	NR	1 (0.3)	2 (0.6)	NR	5 (1.5)	1 (0.3)	1 (0.3)	NR
	PBO + cDMARD	651	26	NR	2 (0.3)	2 (0.3)	NR	5 (0.8)	4 (0.6)	3 (0.5)	NR
SELECT-NEXT[40] Burmester, 2018	UPA 15 mg + cDMARD	221	12	12 (5)	0 (0)	0 (0)	9 (4)	1 (<1)	0 (0)	3 (1)	0 (0)
	UPA 30 mg + cDMARD	219	12	12 (6)	2 (<1)	1 (0.5)	7 (3)	3 (1)	3 (1)	6 (3)	0 (0)
	cDMARD	221	12	9 (4)	0 (0)	1	12 (5)	1 (<1)	1 (<1)	1 (<1)	0 (0)
SELECT-BEYOND[48] Genovese 2018	UPA 15 mg + cDMARD	164	12	NR	1 (0.6)	0 (0)	NR	1 (0.6)	1 (0.6)	1 (0.6)	NR
	UPA 30 mg + cDMARD	165	12	NR	2 (1.2)	1 (0.6)	NR	4 (2.4)	2 (1.2)	4 (2.4)	NR
	Placebo + cDMARD	169	12	NR	0 (0)	0 (0)	NR	(0)	0 (0)	1 (0.6)	NR
SELECT-NEXT[40] Burmester, 2018	UPA 15 mg + cDMARD	221	12	12 (5.4)	0 (0)	0 (0)	9 (4.1)	1 (0.5)	0 (0)	1 (0.5)	0 (0)
	UPA 30 mg + cDMARD	219	12	12 (5.5)	2 (0.9)	0 (0)	7 (3.2)	3 (1.4)	3 (1.4)	2 (0.9)	0 (0)
	cDMARD	221	12	9 (4.1)	0 (0)	0 (0)	12 (5.4)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0)

N/A: not available, n: number, N: total number, NR: not reported, Resp.: respiratory, TB: tuberculosis

*Infections and infestations.

Appendix E. Comparative Value Supplemental Information

Table E1. Impact Inventory

Sector	Type of Impact (Add Additional Domains, as Relevant)	Included in This Analysis from… Perspective?		Notes on Sources (if Quantified), Likely Magnitude & Impact (if Not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	☐	☐	
	Future unrelated medical costs	☐	☐	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	☐	
	Transportation costs	NA	☐	
Non-Health Care Sectors				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	☐	
Consumption	Future consumption unrelated to health	NA	☐	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	☐	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al. 2016[108]

hēRo3

hēRo3 compiles information and data that users enter into a browser describing the structure and estimated parameters of a model, sends it to the cloud platform where necessary calculations are performed in heRomod, and then parses information received from the modeling package to various output displays, including Markov traces, bar charts, area charts, tornado diagrams, waterfall charts, efficiency frontiers, and hexbin and contour plots, as well as tabular displays. hēRo3 effectively allows users to build and run models in the programming language, R, even if they have had limited or no experience programming in R. hēRo3 also generates an Excel workbook with every model that provides a detailed listing of all input variables, intermediate calculations, and final output on a cycle-by-cycle basis to facilitate model checking and auditing.

Description of the evLYG Calculations

The cost per evLYG considers any extension of life at the same "weight" no matter what treatment is being evaluated. Below are the stepwise calculations used to derive the evLYG.

1) First, we attribute a utility of 0.851, the age- and gender-adjusted utility of the general population in the US that are considered healthy.[109]
2) For each cycle (Cycle I) in the model where using the intervention results in additional years of life gained, we multiply this general population utility with the additional life years gained (∆LYG).
3) We sum the product of the life years and average utility (cumulative LYs/cumulative QALYs) for Cycle I in the comparator arm with the value derived in Step 2 to derive the equal value of life years (evLY) for that cycle.
4) If no life years were gained using the intervention versus the comparator, we use the conventional utility estimate for that Cycle I.
5) The total evLY is then calculated as the cumulative sum of QALYs gained using the above calculations for each arm.
6) We use the same calculations in the comparator arm to derive its evLY.
7) Finally, the evLYG is the incremental difference in evLY between the intervention and the comparator arms.

DAS28-ESR to DAS28-CRP Conversion for Tofacitinib and Conventional DMARD

We did not find any published data on DAS28-CRP outcomes at three months for tofacitinib and its conventional DMARD comparator. Some trials (SELECT-monotherapy, RA-BUILD, RA-BEACON, and ORAL-STEP) simultaneously reported DAS28-ESR and DAS28-CRP outcomes for upadacitinib, baricitinib, and tofacitinib, and their respective comparators. A simple average of the disease activity proportions using DAS28-CRP and DAS28-ESR data resulted in an approximate 2x and 1.5x ratio of CRP to ESR in the TIM arms, while the conventional DMARD arms showcased more

variability. In the absence of DAS28-CRP trial data at three months, we applied these ratios to the DAS28-ESR data to derive DAS28-CRP data to tofacitinib and its conventional DMARD comparator (Table E2).

Table E2. DAS28-ESR to DAS28-CRP Conversion for Tofacitinib and Conventional DMARD at Three Months

	Proportion of Patients Achieving Different Categories of Disease Activity by DAS28 at Three Months*					
	Tofacitinib			cDMARD		
	<2.6 (Remission)	2.6 to ≤3.2 (LDA)	>3.2 (MDA and HDA)	<2.6 (Remission)	2.6 to ≤3.2 (LDA)	>3.2 (MDA and HDA)
DAS28-ESR	7%	9%	83%	2%	2%	96%
Adjusted DAS28-CRP	15%	14%	71%	5%	3%	92%

cDMARD: conventional disease-modifying antirheumatic drug, CRP: c-reactive protein, DAS28: Disease Activity Score 28, ESR: erythrocyte sedimentation rate, HDA: high disease activity, LDA: low disease activity, MDA: moderate disease activity

*Mutually exclusive categories.

Table E3. Key Undiscounted Health and Economic Outcomes for Upadacitinib versus Adalimumab

Treatment	Drug Cost* (Line One)	Total Cost	LYs	QALYs
Upadacitinib + cDMARD	$78,400	$151,000	25.07	17.46
Adalimumab + cDMARD	$52,600	$123,000	25.05	17.40

cDMARD: conventional disease-modifying antirheumatic drug, evLYG: equal value of life years gained, LY: life year, QALY: quality-adjusted life year

*Only costs of TIM. Does not include cDMARD cost.

Table E4. Key Undiscounted Incremental Cost-Effectiveness Ratios for Upadacitinib versus Adalimumab

Treatment	Cost per LY Gained	Cost per QALY Gained
Upadacitinib vs. Adalimumab	$1.6 million	$448,000

LY: life year, QALY: quality-adjusted life year

Table E5. Key Undiscounted Health and Economic Outcomes for Adalimumab versus Conventional DMARD

Treatment	Drug Cost(Line One)	Total Cost	LYs	QALYs
Adalimumab + cDMARD	$52,600*	$122,600	25.05	17.40
cDMARD	$3,600	$67,600	25.03	17.33

cDMARD: conventional disease-modifying antirheumatic drug, LY: life year, QALY: quality-adjusted life year

*Cost of TIM alone.

Table E6. Key Undiscounted Health and Economic Outcomes for Tofacitinib versus cDMARD

Treatment	Drug Cost (Line One)	Total Cost	LYs	QALYs
Tofacitinib + cDMARD	$42,400*	$112,500	25.05	17.39
cDMARD	$2,300	$66,500	25.03	17.31

cDMARD: conventional disease-modifying antirheumatic drug, LY: life year, QALY: quality-adjusted life year
*Cost of TIM alone.

One-Way Sensitivity Analyses

Table E7. One-Way Sensitivity Analyses of Upadacitinib versus Adalimumab for QALY Outcomes

Parameters	Low Input	High Input	Low Value	High Value
Baseline HAQ	1.76	1.44	11.010	12.501
Utility (Mapped from HAQ)	Multiple	Multiple	11.448	12.080
Probability of Remission with Upadacitinib at Three Months	26.5%	31.5%	11.759	11.779
Rate of Serious Infection with Palliative Care	0.02	0.034	11.770	11.768
Disutility of Serious Infection	0.14	0.17	11.770	11.769
Rate of Serious Infection with TIMs	0.027	0.046	11.769	11.769

HAQ: Health Assessment Questionnaire, TIM: targeted immune modulator

Table E8. One-Way Sensitivity Analyses of Upadacitinib versus Adalimumab for Total Cost Outcomes

Parameters	Low Input	High Input	Low Value	High Value
Hospitalization Rate (HAQ Range Dependent)	Multiple	Multiple	$98,273	$176,222
Cost of Hospitalization	$1,975.68	$2,963.52	$117,622	$129,079
Probability of Remission with Upadacitinib at Three Months	26.50%	31.50%	$119,282	$127,419
Baseline HAQ	1.76%	1.44%	$123,582	$115,731
Cost of Physician's office Visit	$60.26	$90.38	$122,328	$124,372
Cost of Hepatitis Panel	$52.12	$78.18	$122,466	$124,234
Cost of TB Screening	$67.86	$101.80	$123,056	$123,645
Cost of Lipid Panel	$11.69	$17.53	$123,152	$123,549
Cost of Metabolic Panel	$8.92	$13.38	$123,199	$123,502
Cost of CBC	$8.52	$12.78	$123,206	$123,495

CBC: complete blood count, HAQ: Health Assessment Questionnaire, TB: tuberculosis

Probabilistic Analyses

Figure E1. Probabilistic Analyses: Upadacitinib versus Adalimumab: Incremental Cost-Utility Ratio HexBin